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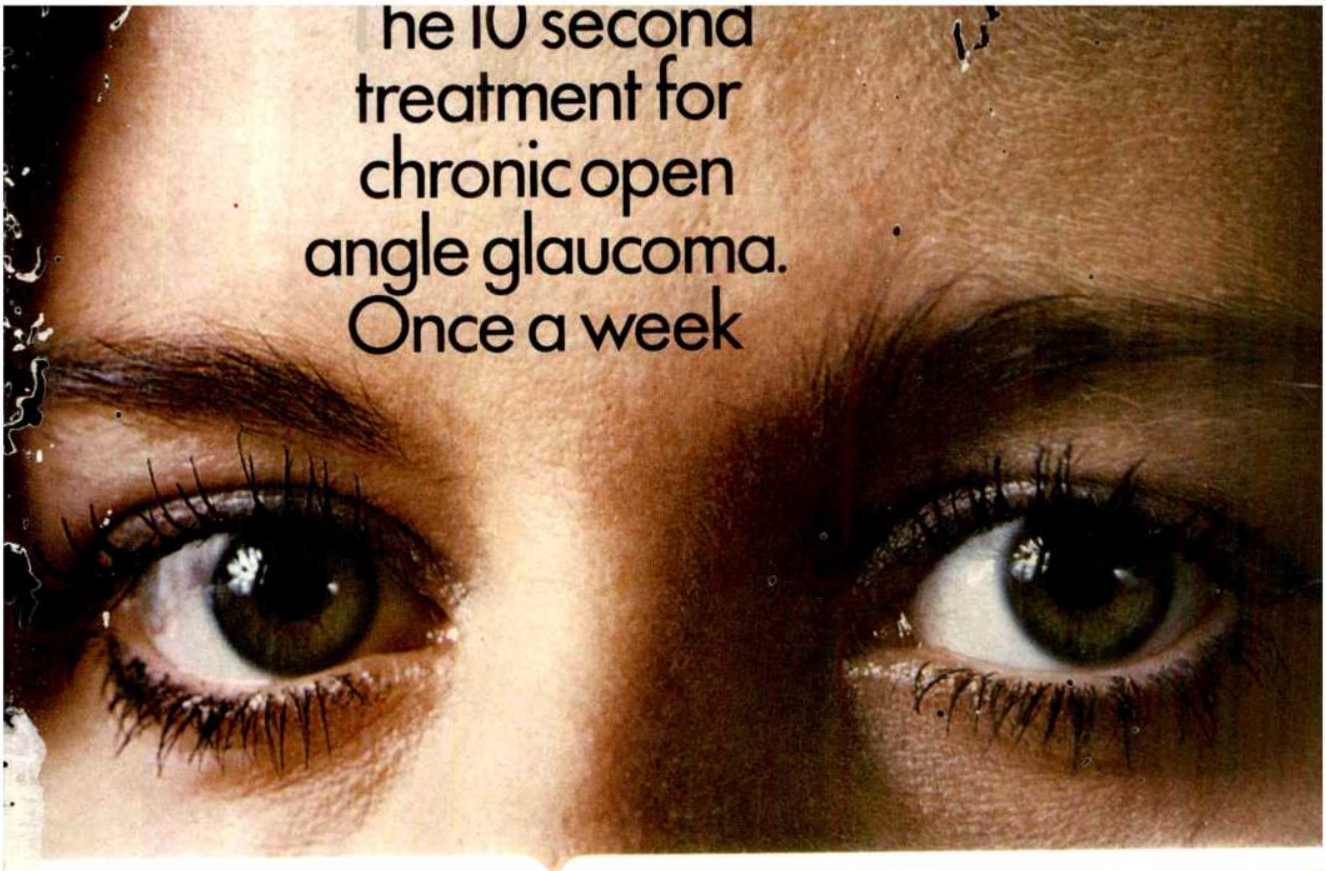

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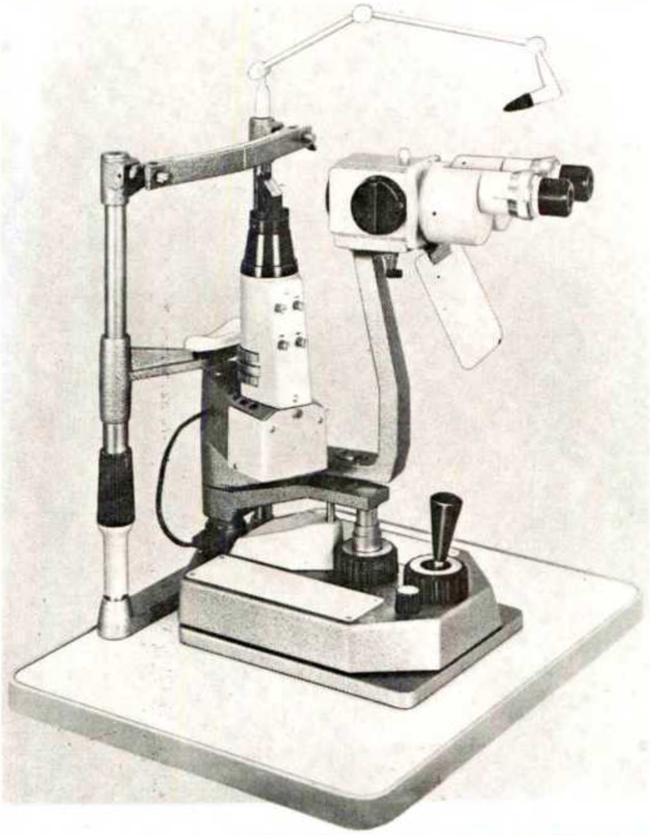

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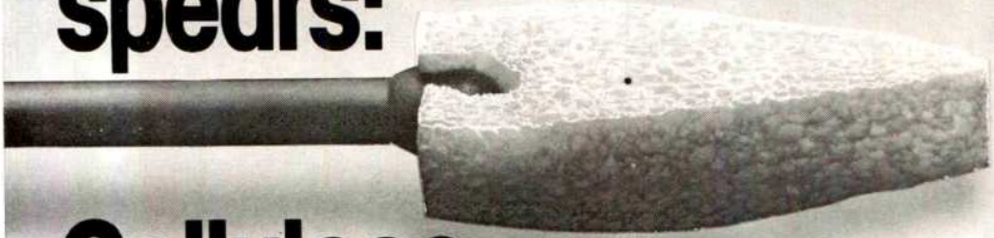

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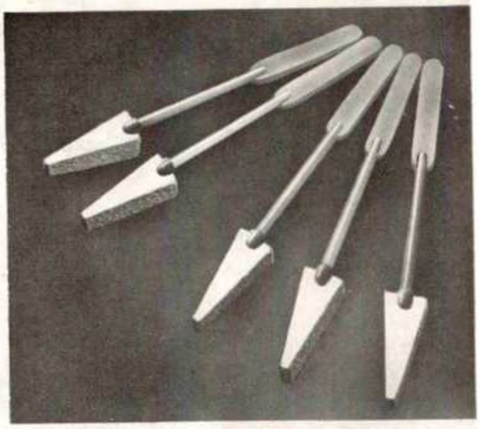

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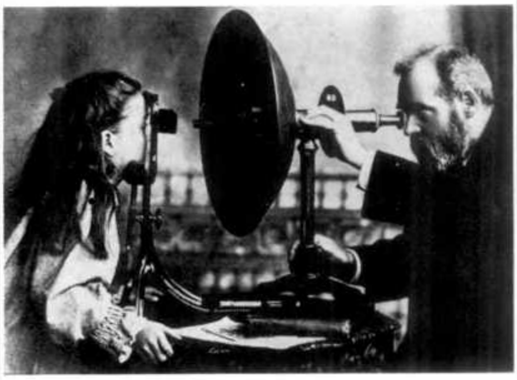

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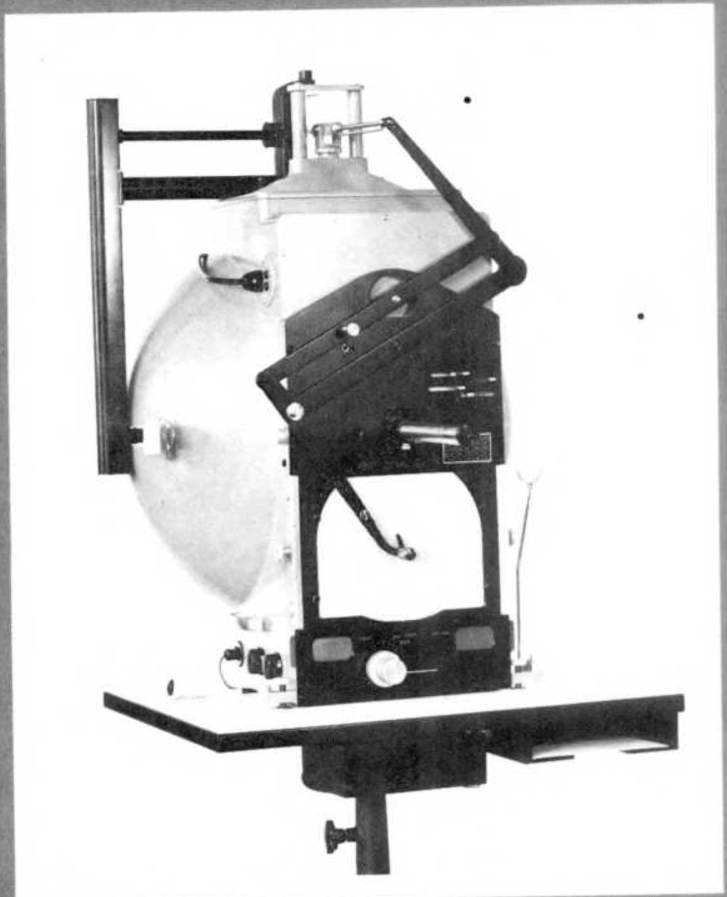

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Editorial: Outflow pathways

The conventional outflow pathway through the trabecular meshwork and Schlemm's canal to the episcleral venous system is the major route by which aqueous humour leaves the intraocular cavities of the eye and accounts for some 90% of total drainage in the human. The fluid which passes by this route must negotiate the intratrabecular and extracellular spaces of the meshwork to reach the endothelium of Schlemm's canal. These spaces become progressively narrower and more tortuous as Schlemm's canal is approached. In the narrowest and most tortuous portion of the system, called the *endothelial meshwork*, the trabecular organisation is lost and is replaced by a loose connective tissue. The extracellular spaces through which the aqueous humour flows contain both coarse framework (collagen and elastic-like components) and fine framework (mucopolysaccharides) extracellular materials. It is this tissue which is thought to offer the greatest resistance to aqueous outflow in the normal eye (Bill and Svedbergh, 1972) and has been implicated as a likely site at which abnormally increased resistance develops in the early stages of primary open-angle glaucoma.

The precise pathway by which the aqueous humour crosses the endothelium lining the trabecular aspect of Schlemm's canal to enter the lumen of this vessel has long been a subject of extensive investigation and much controversy. Certainly it seems to be the case that the endothelial cells are connected to each other by junctions which are not physiologically 'tight', and, as a consequence, some aqueous must leak through the monolayer by this route. However, it has been estimated that the intercellular pathway can account for only 1% of drainage at normal levels of intraocular pressure (Bill, 1975). There is a broad consensus of opinion that the major outflow pathway is a series of temporary transendothelial pores (Bill, 1975; Tripathi, 1977; Grierson, *et al.*, 1978, for reviews). The pores are usually, but not exclusively, found in bizarre outpouchings of the endothelium which are a characteristic feature of this tissue and have been called *giant vacuoles*. These structures are not vacuoles as such, because the vast majority can be shown to be blind invaginations from the meshwork surface of the endothelium. A small proportion also have an opening on the luminal surface of the endothelial cells and are therefore the channels which have been implicated in the transendothelial transfer of fluid. The reason why only a small proportion of the vacuoles are through-and-through channels is poorly understood, but a possible explanation has been provided by Tripathi (see Tripathi (1977) for a recent review). He has suggested that the transcellular channel is a stage in a cyclical process whereby an invagination forms, expands, and becomes a transcellular channel, and then eventually this channel collapses. Little is yet known about the morphogenesis of these structures, but it would seem highly probable that the two factors of greatest importance are (*a*) the pressure head across the endothelium acting as the driving force for vacuolation (Inomata *et al.*, 1972; Grierson and Lee, 1975; Tripathi, 1977), and (*b*) the resilience of the endothelial cell to resist the distorting effect of vacuole formation (Grierson and Lee, 1975).

The conventional outflow system has a high facility of aqueous outflow, that is, it is particularly pressure-sensitive. By way of comparison the uveoscleral subsidiary drainage pathway, which drains aqueous laterally between the bundles of the ciliary muscle to the suprachoroid and accounts for most of the remaining 10% of outflow from the human eye, has a very low facility of aqueous outflow. In an experiment conducted on the cynomolgus monkey Bill (1966) found that, when intraocular pressure was increased from 11 to 22 mmHg, flow through the conventional drainage pathway increased 5-fold, whereas the increase in flow through the uveoscleral pathway was minimal.

Experimental studies of the effects of various levels of intraocular pressure on the morphology of the conventional pathway provide an explanation for its high facility. With stepwise increases of the intraocular pressure within the near physiological range the meshwork, and in particular the endothelial meshwork, becomes progressively distended, and thus the pathways for the passage of fluid become wider. In addition there is a progressive increase in the incidence of giant vacuoles and vacuolar transcellular channels. Therefore when the intraocular pressure is increased the meshwork adopts a configuration which is conducive to the easier passage of fluid through the system. This valve action seems to be purely a passive response, because the changes in both the configuration of the meshwork and the numbers of giant vacuoles can be produced equally well in vitro (Johnstone and Grant, 1973) as in vivo (Grierson and Lee, 1974).

That the pliability of the cells and extracellular elements are important to the normal functioning of the outflow system is highlighted by flow studies through aldehyde-fixed tissue. Aldehyde fixation reduces pliability of the meshwork cells, turns the ground substances of the endothelial meshwork into a cross-linked immobile network, and presumably 'freezes' the vacuole and pore populations of the canal endothelium. Under such circumstances the rate of aqueous outflow and the facility are drastically reduced (Johnstone and Grant, 1973). On the other hand the perfusion of cytochalasin B (which disrupts intracellular microfilament systems) into the anterior chamber results in a marked increase in the facility of aqueous outflow. Interestingly the morphological effect of the drug is to produce distension of the endothelial meshwork and enlarged vacuoles and more numerous pores in the endothelium of Schlemm's canal (Svedbergh *et al.*, 1978).

Clearly the cytoskeletal framework of the cells of the conventional outflow system plays a key role in the pressure-sensitive valve action of this tissue. It is therefore of importance that the actin microfilament, intermediate filament, and microtubule systems of both the canal endothelial cells (giant vacuole formation) and the trabecular meshwork cells (general pliability) are investigated in some detail (see Ringvold, 1978; Grierson and Rahi, 1979). Indeed, the possibility that subtle qualitative or quantitative changes to these cytoskeletal elements, which would radically alter the mechanical properties of the cells, may be a factor in the development of open-angle glaucoma is worthy of consideration.

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Microfilaments in the cells of the human trabecular meshwork

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SUMMARY In this present study the results are presented of a combined ultrastructural and immunofluorescent investigation of 'smooth muscle' elements within the cytoplasm of human trabecular meshwork cells. The cytoplasm of human meshwork cells both *in vivo* and *in vitro* is replete with 10 nm intermediate filaments and also contains smaller 6 nm filaments which are particularly prominent in the cell processes. By immunofluorescence using sera rich in antibodies to contractile proteins, particularly actin, cultured meshwork cells showed strong cytoplasmic fluorescence. On occasion the cytoplasmic fluorescence was diffuse, but more often recognisable bundles (stress fibres) or a loose fibrillar framework was found. The possible role of structural and contractile cellular proteins in trabecular function was discussed.

It has been shown that trabecular meshwork cells are extremely pliable, and in experimentally induced acute increase of intraocular pressure (Grierson and Lee, 1975; Kayes, 1975; Svedbergh, 1976) or after the application of topical pilocarpine (Grierson *et al.*, 1978) these cells are capable of pronounced attenuation without loss of cell-to-cell contact. Grierson and Lee (1975) suggested that cytoskeletal elements and, in particular, the cytoplasmic microfilaments could be expected to have a key role in cellular pliability, and thus they will have an important function in the maintenance of tissue integrity.

Further, it is known that the structural cytoplasmic proteins of many non-muscle cells, in addition to having cytoskeletal functions, can play a part in cellular mobility and contraction (Pollard and Weihing, 1974). If contractile proteins are a component of the cytoplasm of trabecular meshwork cells, it could be expected that filament-dependent cellular contraction may have an influence on outflow dynamics (Inomata *et al.*, 1972). Indeed it has been shown that the intraocular infusion of cytochalasin B, which disrupts contractile cytoplasmic microfilament systems, produces a marked increase in the facility of aqueous outflow (Kaughman and Barany, 1977).

Clearly structural and contractile cytoplasmic proteins may be of some importance to trabecular function. Therefore the present investigation was conducted to determine the nature and distribution of cytoplasmic microfilaments in the cells of the normal human trabecular meshwork, and an attempt was made to demonstrate the presence of contractile protein antigens within cultured human trabecular meshwork cells by means of an immunofluorescent technique.

Materials and methods

NORMAL TISSUE

Normal angular tissue for electron microscopy was obtained from 11 human eyes enucleated in treatment of malignant melanoma of the posterior globe. The patients' ages varied between 46 and 76 years. The eyes showed no clinical evidence of abnormalities in the anterior segment. After enucleation they were immersed in 3% phosphate buffered glutaraldehyde and opened by equatorial section; the lenses were removed, and slices of limbal tissue were taken for further processing. After a wash in phosphate buffer the limbal segments were post-fixed in phosphate buffered osmium tetroxide, rewashed in buffer, dehydrated through graded alcohols, cleared with propylene oxide, and embedded in Araldite.

TISSUE CULTURE

The globes for tissue culture were provided by the eye bank and were used from 6 to 48 hours post mortem. The anterior segment of each eye was divided into quadrants, and the iris and ciliary body were removed under the dissecting microscope. Two

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parallel cuts were made in the trabecular region, and the strip of drainage tissue was carefully removed with minimal handling. The trabecular meshes were transferred to the cover glass of a tissue culture chamber and embedded in an embryonic plasma clot. The chamber was then sealed and filled with a tissue culture medium. For further details see Tripathi *et al.* (1973).

Outgrowths from the explant spread over the surface of the coverslip, and after 6 weeks to 3 months the primary culture was sufficiently well established for either electron microscopy or immunofluorescent studies. Preparation of the trabecular meshwork cells on the coverslips for electron microscopy was by the technique described by Tripathi *et al.* (1973) and Rahi and Ashton (1978).

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For this part of the investigation the coverslips containing monolayers of cultured trabecular meshwork cells were washed in isotonic saline and fixed in acetone.

Blood from patients with chronic uveitis or intraocular melanoma containing high titres (greater than 1/160) of antibodies to 'smooth muscle' proteins, particularly actin (Rahi *et al.*, 1976; Rahi and Ashton, 1978) were used as the source of antiserum to localised contractile cytoplasmic proteins. The reactivity and specificity of the sera were judged by examination of frozen sections from composite blocks of rat liver, kidney, skeletal muscle, stomach, and salivary gland which had been treated with the sera (Trenchev and Holborow, 1976).

After treatment with the appropriate sera the method outlined by Rahi *et al.* (1976) and Rahi and Ashton (1978) using fluorescein labelled antihuman immunoglobulins was adopted. A Zeiss epifluorescence microscope equipped with a fluorescein isothiocyanate interference filter was used for routine examination of the tissues.

Results

ULTRASTRUCTURE

The trabecular meshwork cells of the normal human outflow apparatus contained 2 types of cytoplasmic microfilaments of indeterminate length but of different diameters. The larger filaments measured 10 nm in diameter and were most abundant in the main cell body and in the perinuclear zone (Fig. 1). The 10 nm filaments were formed into either sporadically distributed bundles (Fig. 2) or, more commonly, a subcortical network, so that in any one section the filaments were cut both in cross section and in longitudinal section (Fig. 1). These filaments did not make contact with the plasma membrane but did come into close association with the limiting membranes of some cytoplasmic organelles (Fig. 1).

The finer, more delicate filaments measured between 5 and 6 nm in diameter and were found in loose aggregates throughout the cell cytoplasm from the perinuclear zone to the cell periphery. The fine filaments were particularly prevalent in the cell processes, where they were orientated so that they formed an array which ran parallel with the long axis of the cytoplasmic projection (Fig. 3). Unlike the larger filaments the fine filaments came into close proximity with the plasma membrane (Figs. 3 and 4).

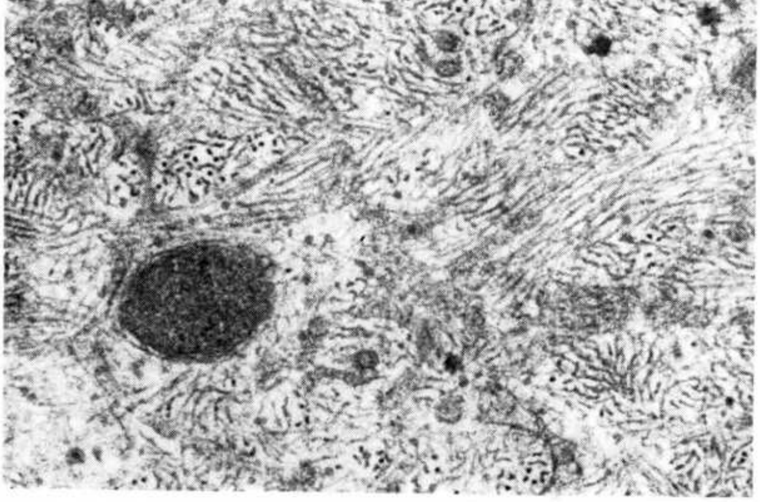

Fig. 1 *Electron micrograph showing 10 nm microfilaments in the cytoplasm of a trabecular meshwork cell. The microfilaments form a network and can be seen both in cross and in longitudinal section* (× 60 000)

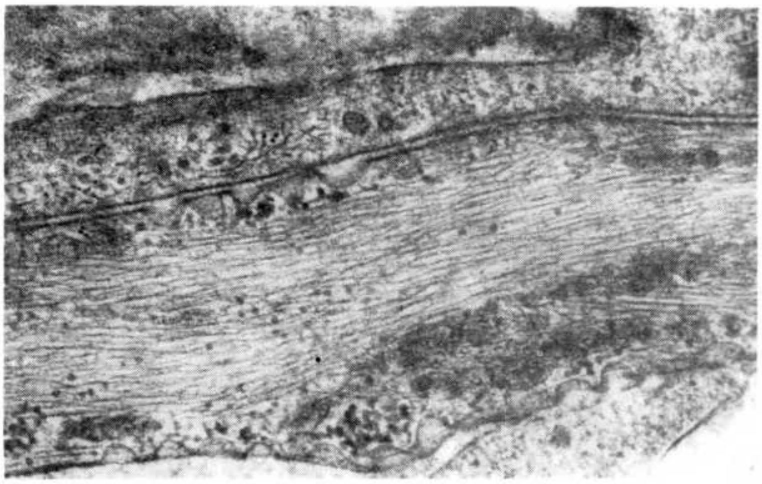

Fig. 2 *Electron micrograph showing a bundle of 10 nm microfilaments in the cytoplasm of a trabecular meshwork cell* (× 50 000)

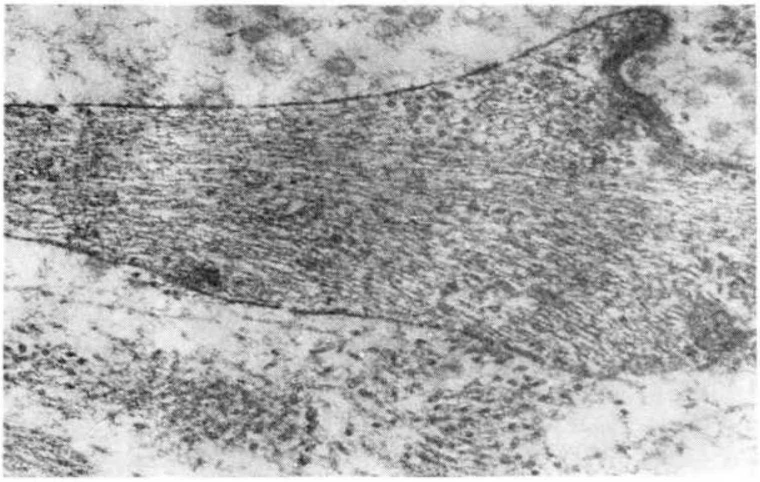

Fig. 3 *Electron micrograph showing abundant 6 nm microfilaments in a cytoplasmic process of a trabecular meshwork cell* (× 68 000)

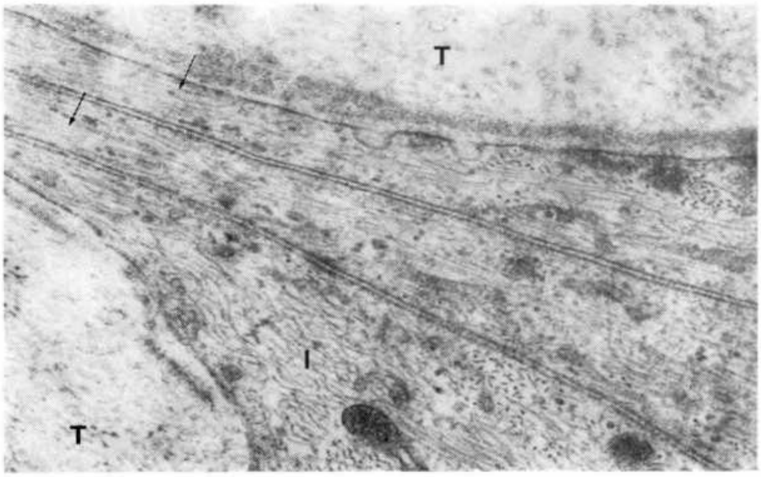

Fig. 4 *Electron micrograph of trabecular meshwork cells, trabecular cores indicated* (T). *In one cell 10 nm intermediate microfilaments predominate* (I), *whereas in the others 6 nm microfilaments can be seen (arrows)* (× 40 000)

Studies of the fine structure of cultured trabecular meshwork cells revealed the presence of both types of cytoplasmic microfilament previously described.

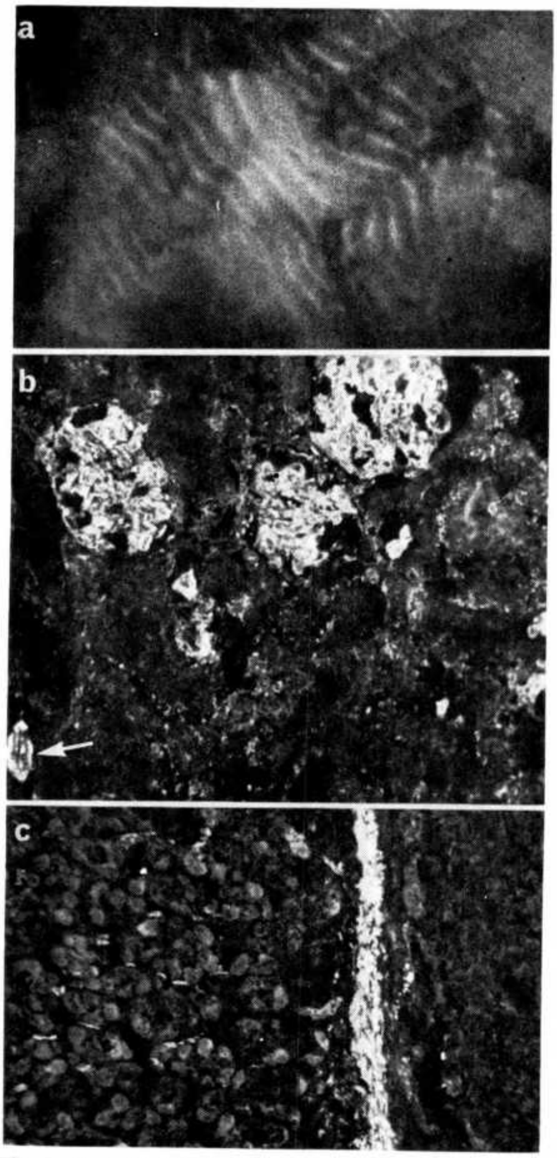

Fig. 5 *Indirect immunofluorescence tests on cryostat sections of rat tissues.* (a) *The anti-actin antibody in the sera reacts at the 'I' band to produce distinctive fluorescence in skeletal muscle* (×1100). (b) *A section through the wall of the stomach shows bright fluorescence at the muscularis mucosa and also in the muscle fibres between the gastric glands* (×190). (c) *In a section of kidney the sera have reacted with contractile proteins of cells in the glomeruli and in the wall of an artery (arrow)* (×190)

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From the multiple blocks the skeletal muscle showed specific fluorescence for the 'I' bands (Fig. 5*a*). The muscle fibres between gastric glands were strongly fluorescent (Fig. 5*b*), as were the glomeruli and peritubular tissue of the kidney (Fig. 5*c*). In addition hepatocytes showed a polygonal staining pattern. On the basis of these findings it was evident that the sera used reacted strongly with cells which are known to have an abundance of 'smooth

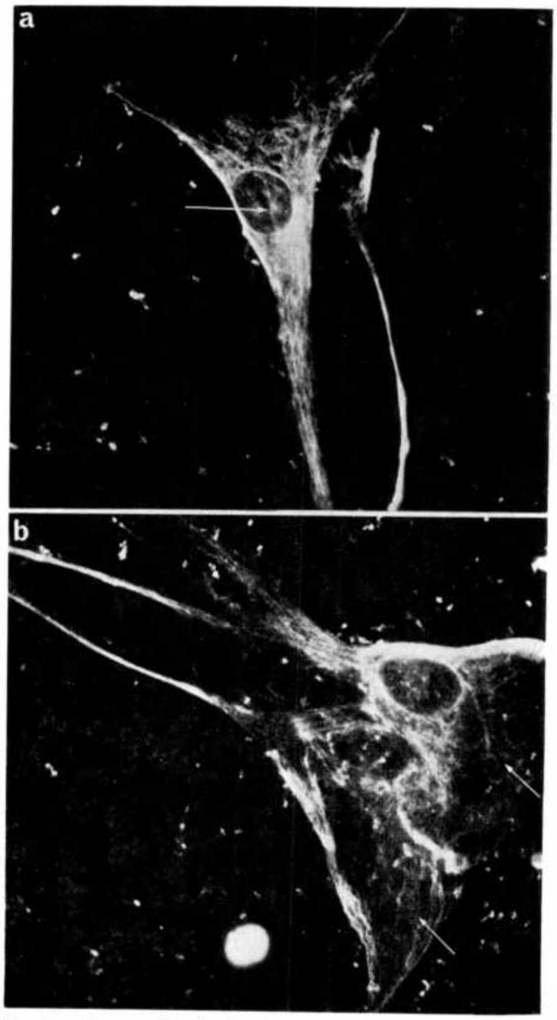

Fig. 6 *Acetone fixed cultured trabecular meshwork cells tested by the indirect immunofluorescence with anti-'smooth muscle' sera.* (a) *Strong cytoplasmic fluorescence in a meshwork cell. Note the unstained cell nucleus (arrow)* (×520). (b) *Two meshwork cells in which there is strong fluorescence in the long extended cell processes. A fluorescence-positive network can be seen in the main cell body (arrow)* (×520)

muscle' proteins and to be particularly rich in actin.

When cultured trabecular meshwork cells were treated with the sera, there was a strongly positive cytoplasmic fluorescence. Cytoplasmic fluorescence was particularly prominent in the cell processes (Fig. 6), at the cell margin, and as a perinuclear halo. At higher magnification recognisable fibres or bundles were found both in the main cell body (Fig. 7*a*) and in the cellular processes (Fig. 7*b*). The bundles were orientated so that they ran parallel with the long axis of the cell, and similar bundles have been described in other cell types, where they have been called 'stress fibres' (Wessells *et al.*, 1971). Stress fibres were not found in all the cells examined; in some there was only diffuse cytoplasmic staining, whereas in others a loose fibrillar framework could be identified (Fig. 6).

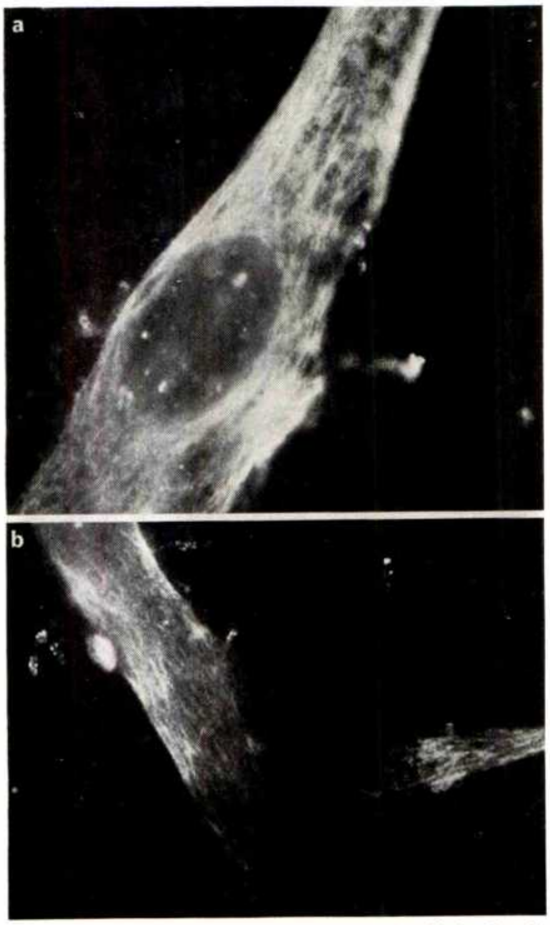

Fig. 7 (a) *Part of a trabecular meshwork cell fixed with acetone and tested by indirect immunofluorescence using serum which contains anti-'smooth muscle' antibody. Subcortical bundles of actin-containing filaments can be seen* (×935). (b) *A trabecular meshwork cell process from a culture which was fixed in acetone and treated with serum containing anti-'smooth muscle' antibodies. Bundles or sheaths of contractile protein are evident* (×765)

Discussion

The cytoplasm of human trabecular meshwork cells is rich in 6 and 10 nm microfilaments. The 6 nm microfilaments were most numerous at the cell periphery, round the cell nucleus, and within cytoplasmic processes. It was therefore of interest to note that the forementioned sites showed, in most meshwork cells, the strongest fluorescence after exposure to sera rich in antibodies to actin and other contractile proteins.

Recently Ringvold (1978) was able to identify 4·5 to 6·5 nm cytoplasmic filaments in the trabecular meshwork cells of the vervet monkey. He exposed glycerinated segments of trabecular meshwork to myosin subfragment (S-1), which forms characteristic 'arrowhead' complexes with actin containing microfilaments. Ringvold found that 'arrowhead' complexes were prevalent on the 4·5 to 6·5 nm diameter filaments and suggested that they were therefore actin filaments. Actin in conjunction with myosin is involved in cellular contraction and motility but also plays a part in other biological functions such as phagocytosis, pinocytosis, and cell adhesion (Allison *et al.*, 1971; Malawista *et al.*, 1971; Wessells *et al.*, 1971; Pollack and Rifkin, 1975; Tilney, 1975).

However, the predominant cytoskeletal component of human trabecular meshwork cells was shown to be 10 nm diameter filaments. These so-called intermediate filaments are of uncertain chemical identity (Lansing-Taylor, 1975). Only 1 component protein within these structures has been described so far and has been called alternatively desmin or skeletin (Kurki *et al.*, 1977). It has been suggested that typically they do not have an actin component (Ishikawa *et al.*, 1969) and that they have a structural rather than a contractile role. On the other hand the distribution of intermediate filaments is altered at the onset of locomotion by leukaemia cells (Felix and Strauli, 1976), and 10 nm filaments in pigment epithelial cells of the retina do contain actin (Burnside, 1976), though this may be an exceptional case. Also 10 nm intermediate filaments are involved in axoplasmic transport in nerve cells (Felix and Strauli, 1976) and have been implicated in the intracellular transport of cytoplasmic organelles in fibroblasts (Goldman and Follett, 1969).

The structural and contractile proteins within trabecular meshwork cells may well be of some importance to trabecular function, since trabecular cell pliability and contraction may influence the width of intertrabecular spaces and hence affect the rate of aqueous outflow (Kaughman, 1977). However, it is also known that trabecular meshwork cells are latent phagocytes, and in various forms of secondary open-angle glaucoma the native cells of the drainage system engulf considerable quantities of debris (Grierson and Lee, 1973; Van Buskirk and Leure-Dupree, 1978). Recently the suggestion has been put forward that primary open-angle glaucoma may arise as a result of an inability of meshwork cells to phagocytose and get rid of the debris which may accumulate in the outflow system of the older eye (Bill, 1975). If this interesting hypothesis is to be tested, clearly it would be worthwhile to embark on further studies of the filament systems within these cells, which, as has been stated previously, are known to have a key role in the phagocytic process.

Although it has been established in the study reported here that contractile proteins are present in human trabecular meshwork cells, more detailed investigations need to be performed to determine which smooth muscle contractile proteins apart from actin are present in these cells and what role they play in cell contraction, anchorage, and phagocytosis in the normal and diseased outflow system.

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The trabecular wall of Schlemm's canal: a study of the effects of pilocarpine by scanning electron microscopy

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SUMMARY The scanning electron microscope was used to study the endothelium lining the trabecular wall of Schlemm's canal in 10 human eyes enucleated in treatment of choroidal melanomas. The eyes of 5 patients had been treated before enucleation with pilocarpine drops, and the remaining 5 were untreated and served as controls. In the pilocarpine-treated tissue there was an increased prominence of cellular bulges in the endothelial monolayer, and the endothelial pores were both larger and more frequent than in the untreated eyes. By the use of Poiseuille's formula it was calculated that the resistance offered by the pore system to the drainage of aqueous in the pilocarpine-treated group was approximately one-ninth of that in the control series.

In a previous investigation the present authors showed by light microscopy and transmission electron microscopy (TEM) that the incidence of giant vacuoles and transcellular pathways in the endothelium of Schlemm's canal was greater in human eyes which had been treated with topical pilocarpine than in a suitable control group of a similar age range (Grierson *et al.*, 1978). This finding was in disagreement with the results of a previous quantitative TEM investigation (Holmberg and Bárány, 1966) in which it was shown that vacuole counts in the endothelium of Schlemm's canal were lower after the topical application of pilocarpine. The experiment of Holmberg and Bárány was conducted on a group of cynomolgus monkeys, and both gross facility and net outflow were increased by the action of the drug. In an attempt to explain their findings Holmberg and Bárány proposed that the vacuolar flow pathways had become less tortuous and that straightening out of the vacuolar channels would account both for the decrease in incidence in single sections and for the increased rate of drainage.

Svedbergh (1976), however, has criticised the use of TEM in the assessment of changes in flow pathways through the lining endothelium of Schlemm's canal. This criticism is largely based on the fact that only a small proportion of giant vacuoles are transcellular channels (Kayes, 1967; Tripathi, 1968, 1971, 1974; Inomata *et al.*, 1972; Grierson and Lee, 1975; Grierson *et al.*, 1978), and it is possible to find transcellular channels which are not associated with a vacuolar swelling (Inomata *et al.*, 1972; Grierson and Lee, 1975).

Quantitative data on the luminal openings of vacuolar and nonvacuolar transcellular channels can be obtained by examining the endothelium lining the trabecular aspect of Schlemm's canal with the scanning electron microscope (SEM). This technique provides a useful means of examining relatively large areas of exposed canal endothelium and overcomes the sampling problem associated with TEM. It was therefore considered appropriate to apply scanning electron microscopy to the study of the material which was used in the initial light microscopy and TEM investigation of the effects of pilocarpine in the human outflow system. In particular, the analysis was directed towards the variation in incidence and size of the luminal pores in the endothelium of the treated and untreated tissue.

Materials and methods

The tissue for this investigation came from 10 patients with an ostensibly normal anterior segment, and each eye was enucleated in treatment of a choroidal melanoma. With 5 patients the eye to be enucleated was subjected to a topical application of 2 to 4% pilocarpine on 4 separate occasions at 6-hourly intervals before surgery. The remaining 5 patients were untreated, and the tissue served as a control. On enucleation the eyes were immersed in 2 to 4% glutaraldehyde in phosphate buffer. There-

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after blocks of limbal tissue were removed, washed in buffer, postfixed in 1% buffered osmium tetroxide, and washed again in phosphate buffer.

The technique for dissection of the trabecular wall of Schlemm's canal has been described previously (Lee, 1971). With a ground razor blade a cut was made from the anterior limit of the canal across the peripheral cornea and into the supraciliary space from the posterior portion. The dissection leaves 2 pieces of tissue, one which shows the surface of the scleral sulcus and the other the endothelium of the trabecular wall.

The tissue was freeze-dried in a Balzars Micro BA3 unit which maintained a vacuum of 10^{-5} Torr. Before water extraction the tissue was passed through liquid Arcton[12] and frozen in liquid nitrogen. The dried tissue was coated with gold in a Polaron Sputter Coater E5000 and examined in a Cambridge Stereoscan S600.

For the quantitative analysis of endothelial porosity coded pieces of tissue from pilocarpine treated and untreated eyes were processed in parallel to minimise variation in preparation. Mapping photographs of the endothelial monolayer were taken at a screen magnification of ×3000 and enlarged to a print size which corresponded to an area of 2500 μm². The number of cellular bulges and surface openings were recorded on coded photomicrographs, and the total area examined in each eye was between 250 000 and 400 000 μm². Maximum pore widths were measured from sets of prints which corresponded to a surface area of 100 000 μm² with the use of a ×7 magnifier which incorporated a calibrated graticule.

Results

Examination of the dissected portions of Schlemm's canal from both the treated and untreated eyes showed that the general topography of the endothelium lining the trabecular aspect of the canal was similar to previously published findings (Hoffmann and Dumitrescue, 1971; Bill and Svedbergh, 1972; Segawa, 1973). In some regions the endothelium was flat, whereas in others there were distinct ridges, humps, and areas of disruption where septa had been torn. The individual cells of the endothelial monolayer were elongated and spindle shaped, and each had a prominent central ovoid bulge (Fig. 1).

Each bulge contained the endothelial cell nucleus and possibly a giant vacuole, but, in adequately prepared tissue, identification of the giant vacuoles was speculative except where the delicate vacuolar shell was mechanically disrupted during dissection to reveal its hollow interior. If this disruption was sufficiently extensive the meshwork pore at the base of the cystic cavity was exposed (Fig. 2).

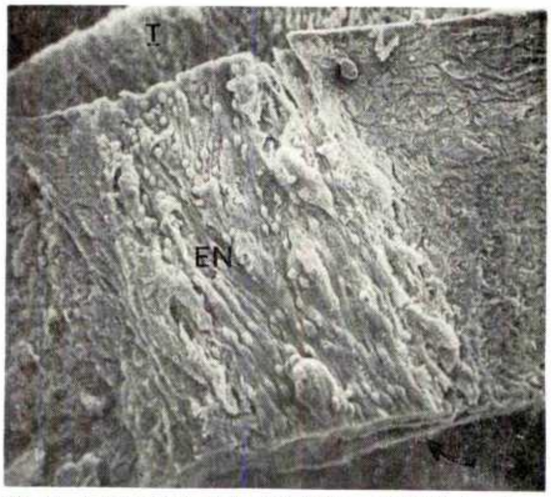

Fig. 1 *A dissection of the endothelium (EN) lining the trabecular aspect of Schlemm's canal in an untreated eye. The trabecular meshwork is indicated by an arrow. The iris (I) is seen beneath the trabecular meshwork (arrow)* (×120)

Openings with a smooth outline were found both on and off the bulges. As in previous reports of Bill (1970), Bill and Svedbergh (1972), Segawa (1973), and Lee and Grierson (1975), the former were considered to be the lumen pores of giant vacuoles and the latter to be the openings of nonvacuolar transcellular channels (Fig. 2). The distributions of both types of pore were not uniform, and areas of particular abundance and also areas of deficiency were common to both the eyes treated with pilocarpine and the untreated tissue. Surface pitting was also found to a greater or lesser extent, both on and off the bulges. This was an artifact which may have been produced by the crystallisation of surface deposits (plasma) during the freeze-drying, and this was a troublesome feature because the largest pits could have been mistaken for pores. Therefore the identification of true pores was not always clear-cut, but with care and critical evaluation most of the artifacts could be eliminated. In addition the study was essentially relative, and it was assumed that the preparation hazards were equally applicable to the treated and the untreated tissues.

There were qualitative differences in the endothelial bulges which protruded from the endothelial cells of the monolayer between the treated and untreated tissue. In the pilocarpine treated tissue the cellular bulges occupied a larger portion of the monolayer. They protruded further into the canal and were often seen as smooth-walled spherical

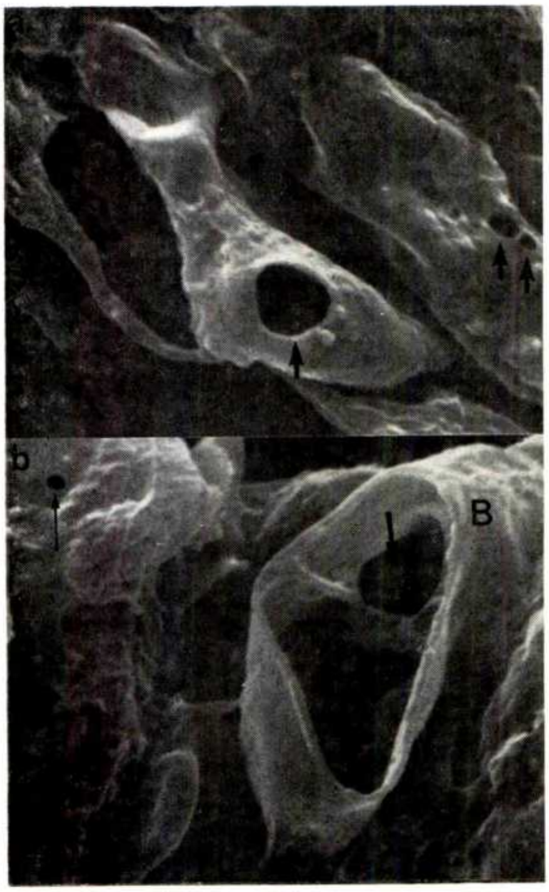

Fig. 2 (a) *Pores in endothelial bulges (arrows) from the trabecular wall of Schlemm's canal in an untreated eye* (× 3800). (b) *A bulge (B), which has a large artifactual opening, in the trabecular wall endothelium of Schlemm's canal in an untreated eye. The bulge appears to be hollow and a meshwork pore (arrow) is evident at the base of the cavity. Note the non-bulge pore elsewhere in the endothelium (small arrow)* (× 3800)

grape-like structures, whereas the bulges in the untreated tissue were usually less obtrusive, more ovoid, and sometimes had a rough crenated surface (Fig. 3). The bulges in the treated tissue were more prone to total or partial collapse (the action of surface tension forces during the drying process) and to artifactual tearing than in the untreated tissue. Presumably this was due to the presence of particularly large giant vacuoles with delicate and therefore vulnerable cytoplasmic shells.

It was our impression that pores both on and off the bulges were more in evidence in the pilocarpine-treated series than in the untreated group. However, there was considerable variation within both groups, and a quantitative analysis was undertaken to determine in as precise a manner possible the effects of pilocarpine on the canal pores of the endothelial flow pathways.

QUANTITATIVE ANALYSIS

Three structural features were counted in the endothelial monolayer: (*a*) bulges (since some contained giant vacuoles), (*b*) openings on the bulges, and (*c*) openings elsewhere on the endothelial cells.

There were three major sources of error or inaccuracy in the quantitative analysis. (*a*) True pores were defined as openings with a regular and smooth outline to distinguish them from ragged deficits which resulted from the preparation. However, the distinction was not always clear-cut and therefore an overcount was possible. Conversely, true pores may have been damaged and were thus eliminated from the count. (*b*) Particular difficulty was encountered with pores outside the openings which could have been obscured by grooves and ridges in the monolayer. (*c*) The analysis was based on viewing from one angle only, so that inevitably a proportion of the openings would have been missed.

In view of these problems in analysis a check was carried out on duplicate photographic prints to assess interobserver differences. The difference was found to be 8% for counts of bulges and 15% for counts of endothelial pores. Table 1 shows that there was no significant difference in the numbers of cellular bulges between the treated and untreated groups. However, there were substantially greater numbers of endothelial pores both on and off the bulges to the extent that there were nearly three times as many in the pilocarpine treated as in the untreated group.

Measurements of maximum pore diameters were made without stereoscopic correction. Without correction a pore will appear erroneously smaller than its 'true' size, the error depending on the tilt of the pore relative to the viewing angle and the direction of its long axis relative to the viewing direction. Since this error was common to the measurements of pore dimensions in both groups, comparison between the 2 groups could be justified. There was a much smaller population of pores in the untreated than in the pilocarpine-treated series, and the histograms (Fig. 4) showed that in both groups the populations were not normally distributed but had a distinct skew, with smaller pores predominating. The mean pore diameters in the pilocarpine-treated eyes were slightly larger than in the untreated eyes. The average diameter of the pores in the control group was 0·9 μm and in the pilocarpine-treated series was 1·3 μm.

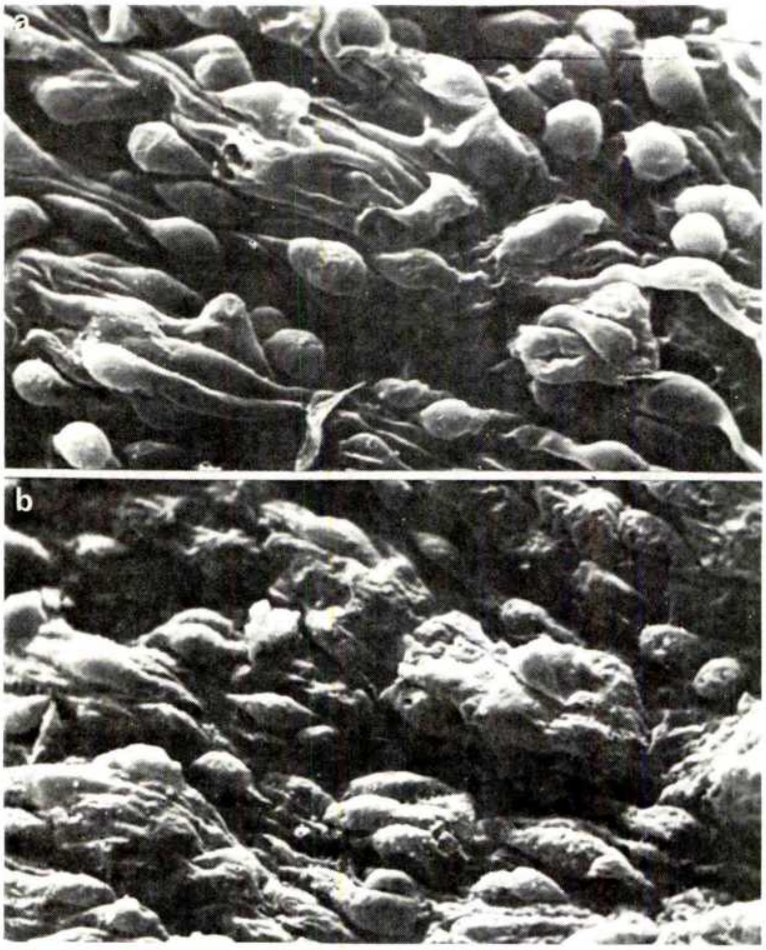

Fig. 3 *The endothelium lining the trabecular aspect of Schlemm's canal in* (a) *a pilocarpine treated and* (b) *an untreated eye. In the pilocarpine treated tissue the endothelial bulges are smooth walled spherical grape-like structures, whereas the bulges in the control are less obtrusive and more ovoid* (× 700)

Table 1 *Results (expressed per square millimetre) obtained from the morphological analysis of surface structures in the lining endothelium of the trabecular wall of Schlemm's canal*

Patient no.	*Age*	*Sex*	*Bulges*	*Pores on bulges*	*Percentage bulges with pores*	*Pores outside bulges*	*Total pores in endolelium*
Treated							
1	46	M	5690	370	7	130	500
2	50	F	4730	900	19	380	1280
3	60	F	4630	1050	23	340	1390
4	61	F	4670	760	16	210	970
5	75	M	4970	460	9	210	670
Mean ± SD			4970 ± 450	710 ± 290*	15 ± 7	260 ± 100†	960 ± 380*
Untreated							
1	31	F	5740	380	7	160	540
2	63	M	4550	200	4	60	260
3	63	F	4130	220	5	90	310
4	68	F	3340	150	5	75	225
5	75	F	4690	280	6	120	400
Mean ± SD			4490 ± 880	250 ± 90	5 ± 1	100 ± 40	350 ± 130

Levels of significance: *$P < 0{\cdot}001$. †$P < 0{\cdot}01$.

When the pore distributions were pooled and expressed as percentage incidences it was found that there was a distinct difference in the pore distribution profile between the treated and the untreated groups (Fig. 5). Only 3% of the pore population in the pilocarpine-treated series had a diameter greater than 3·0 μm, which was the maximum size found in the control group. However, in the untreated group small pores predominated, and approximately 70% of the population had a diameter of 1 μm or less compared with 45% of the pores in the pilocarpine population. On the other hand less than 9% of the pores from the control population were 1·6 μm or greater, which can be compared with a value of 28% from the pore population in the pilocarpine-treated tissue.

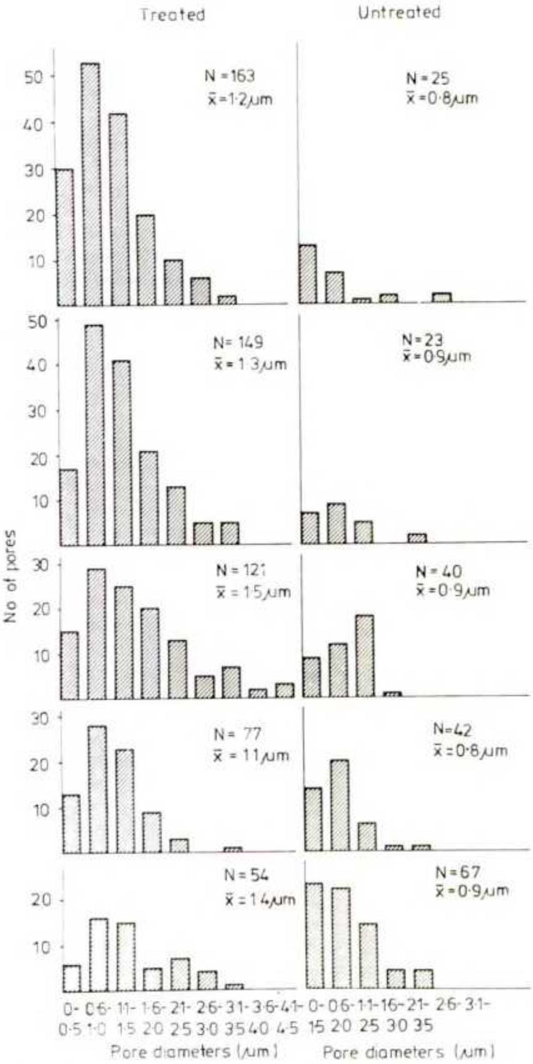

Fig. 4 *The distribution of pores on the basis of their diameters, from a sample area of 100 000 μm² for each of the 10 eyes under investigation. N is the number of pores and x̄ is the mean diameter*

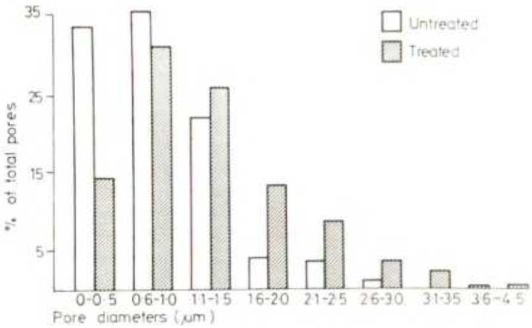

Fig. 5 *The percentage incidence of pores in each of the various size categories from the grouped data from the 5 treated and 5 untreated eyes*

Discussion

The instantaneous 3-dimensional image of the SEM helped to highlight topographical differences in the endothelial monolayer on the trabecular aspect of Schlemm's canal between the pilocarpine treated and the untreated group. In particular it was shown that the endothelial bulges became more pronounced, and the porosity of the endothelium was increased by the action of the drug. The increased prominence of the cellular bulges was probably the result of the increase in size and incidence of giant endothelial vacuoles in the treated eyes (Grierson *et al.*, 1978). Similar findings are associated with increase in intraocular pressure (Grierson and Lee, 1975).

It was of interest to plot the bulge pore incidence obtained in the present study against the appropriate vacuolar counts published in the previous paper (Grierson *et al.*, 1978). From Fig. 6 it can be seen that high counts of bulge pores are associated with high incidences of giant vacuoles. Although the data are insufficient for meaningful statistical analysis, the trend encourages the assumption that the pores in the bulges are the luminal openings of giant vacuoles.

In both groups it was found that the distribution of endothelial pores was nonuniform, there being areas of relative abundance and other regions where pores could not be found. This observation was considered to be further evidence for the proposal that there are preferential flow pathways through the endothelial meshwork to the overlying endothelial monolayer (Rohen *et al.*, 1967; Bill and

Svedbergh, 1972; Grierson and Lee, 1974; Grierson, 1976; Lee and Grierson, 1974, 1975; Svedbergh, 1976).

SEM is particularly suited to the study of the relatively rare and sporadically distributed endothelial pores because of the large areas of tissue which can be examined by this facility. Indeed, it was possible to demonstrate quantitatively that the pores were greater in both numbers and size in the pilocarpine-treated series than in the untreated group. Thus the findings of the present investigation do not support the suggestion by Holmberg and Bárány (1966) that the effect of pilocarpine essentially is to change the shape of the flow pathways rather than to produce alterations in their numbers.

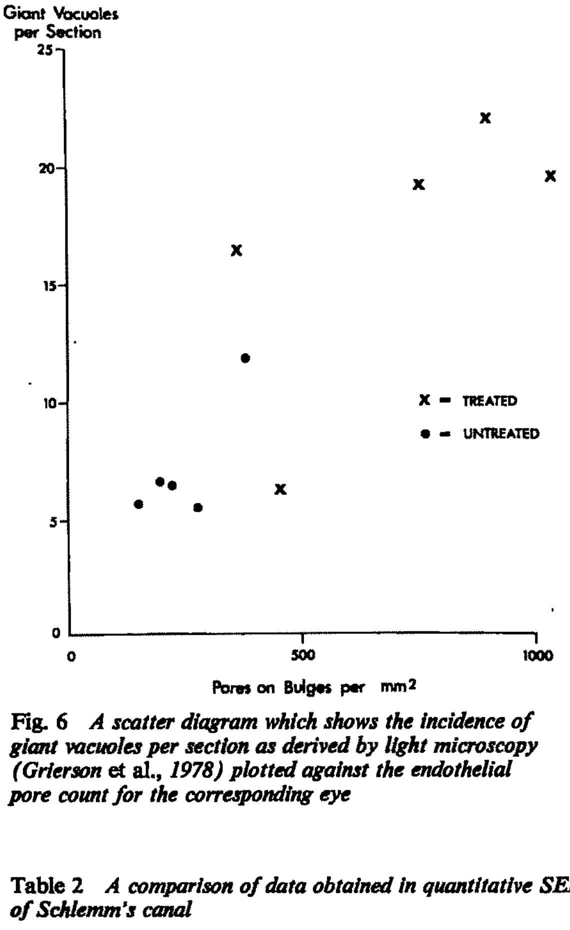

Fig. 6 *A scatter diagram which shows the incidence of giant vacuoles per section as derived by light microscopy (Grierson* et al., *1978) plotted against the endothelial pore count for the corresponding eye*

However, our results must be interpreted with some caution because pore analysis by SEM is not without hazard. Preparation artifacts, like ice crystal formation, tend to produce holes in the endothelial monolayer and raise the pore count, whereas protein masking, produced by the reflux of blood into segments of Schlemm's canal during the trauma of enucleation, tends to cover pores and depress the pore count. Both factors will influence the absolute values obtained in the analysis, but as they were equally likely to occur in treated and untreated tissue they are not considered to invalidate comparison between the 2 groups. In the light of the problems associated with all aspects of preparation of the tissue for SEM it is of value to make comparison between the data obtained from the human control tissue with that obtained by other authors for normotensive humans and monkeys (Table 2).

The incidence of endothelial bulges found from the present study fits reasonably well with the values previously reported. If it is considered that the total surface area of the trabecular wall of Schlemm's canal is 11 mm^2 (McEwen, 1958), then this would give a value from our data of 50 000 for the numbers of bulges, and therefore the cells, which make up the monolayer. Bill and Svedbergh (1972) had a much lower estimate of 23 000 cells in man, but our figure is very close to the 55 000 estimated by Segawa (1973).

The size range of the cellular pores is also in fairly close agreement with the values previously

Table 2 *A comparison of data obtained in quantitative SEM studies of the endothelium lining the trabecular wall of Schlemm's canal*

Author	*Species*	*IOP*	*Bulges/ mm^2*	*Pore frequency on bulges*	*Total pores/ mm^2*	*Pore size in µm*
Bill (1970)	Vervet and Rhesus monkey	Normal	4000	29%	1200	0·3–2·0
Lee (1971)	Rhesus monkey	18–20 mmHg	6000	—	—	0·2–1·0
Hoffman and Dumitrescu (1971)	Human	Normal	—	—	—	up to 2·0
Bill and Svedbergh (1972)	Human	Normal	2000	—	1800	0·15–5·0
Segawa (1973)	Human	Normal	5000	20%	1000	0·15–1·5
Lee and Grierson (1975), Grierson (1976)	Rhesus monkey	15 mmHg	3800	15%	950	0·1–4·0
Svedbergh (1976)	Cynomologus monkey	12 mmHg	—	—	1640	0·25–5·0
Present study	Human	Normal	4500	5%	350	0·2-3·0

reported (Table 2), but our values for the total pore incidence and the frequency of pores on bulges are extremely low. To some extent the difference may be accounted for by the quantitative technique adopted in the present study. The pore incidences were determined from micrographs similar to the method adopted by Lee and Grierson (1975) and Grierson (1976) for the study of pressure effects on pore incidence in the rhesus monkey. Bill and Svedbergh (1972) and Svedbergh (1976), who are the only other investigators to use a detailed quantitative approach to the investigation of endothelial pores, obtained particularly high values for pore incidence, and their counts were made directly from the display screen on the SEM. The use of photomicrographs rather than the display screen has several advantages because coding and 'blind' assessment, repeatability testing, and determination of interobserver error are much more easily achieved. However, an undercount is inevitable because 'true' pores are often more difficult to identify in electron micrographs and viewing was from one angle only, so that pores hidden behind the bulges are missed. On the other hand overcounting due to counting from the same area twice would be less likely from photomicrographs than from the display screen.

With the possibility of overcounting in the technique adopted by Bill and Svedbergh (1972) and undercounting by the present approach it would seem reasonable that a value somewhere between 350 and 1800 pores per mm^2 (4000 and 20 000 respectively for the whole canal) will approach the true incidence in the older human eye. To some extent the large discrepancy is probably also due to the fact that the tissue in both investigations was fixed by immersion without pressure maintenance. It has been reported that immersion fixation is the least satisfactory technique for the study of temporary pressure-sensitive pathways, which may be radically altered in the time interval between enucleation and penetration of the appropriate layers of tissue by fixative (Grierson, 1976; Svedbergh, 1976).

It is of interest to consider the present results in terms of fluid conductance in order to assess the capacity of the canal endothelium to facilitate the drainage of aqueous humour. The fluid conductance, C (μl min^{-1} mmHg^{-1}) of a pore is the flow, Q (μl min^{-1}) of fluid through the pore per unit drop in pressure, ΔP (mmHg) across the pore.

$$C = \frac{Q}{\Delta P} \tag{1}$$

The mathematical approaches to problems of conductance in such a complex biological system as in the canal endothelium are to be considered in more detail in a later paper. However, the model proposed by Bill and Svedbergh (1972) is suitable for a general estimation of the properties of conductance in the lining endothelium. Bill and Svedbergh represented the pore as an opening 0·3 μm long and of various diameters as measured.

Fluid conductance through a tube is given by Poiseuille's formula:

$$Q = \frac{\Delta P\, r^4}{8\, L \nu} \tag{2}$$

where Q = fluid flow (cm^3 sec^{-1})
ΔP = pressure drop (dynes cm^{-2})
r = radius of tube (cm)
L = length of tube (cm)
ν = fluid viscosity (poise)

It may be shown that, after rearranging the terms and assuming a viscosity of 0·007 poise, which is the viscosity of water, formula (2) may be expressed as:

$$C = \frac{d^4}{l \times 3563} \tag{3}$$

where C = conductance (μl min^{-1} mmHg^{-1})
d = diameter of tube (μm)
l = length of tube (μm)

Flow through an aperture is given by the equation (Happel and Brenner, 1965):

$$Q = \frac{\Delta P\, r^3}{3\nu} \tag{4}$$

It is also possible to rearrange formula (4) and express it more conveniently as:

$$C = \frac{d^3}{2099} \tag{5}$$

According to Bill and Svedbergh the resistance, which is the inverse of the conductance, of each pore may be taken to be the resistance as calculated by formula (3) plus the resistance derived from formula (5). The values obtained for pore conductance and pore resistance by using this approach are shown in Table 3. Because of the small numbers involved, the pore counts in the 5 eyes in both the untreated group and the pilocarpine-treated group have been summed together to produce results for an equivalent area of 500 000 μm^2 and extrapolated to 11 mm^2 in each group.

The results are presented when all the pores are included and also when those pores above a diameter of 3 μm have been omitted. Since the large pores have a considerable effect on the conductance, the inclusion of a potential artifact such as a large-diameter pore will greatly increase the calculated conductance. Thus, while the pores of diameter

Table 3 *Calculated values for the conductance and resistance in the pore system in the lining endothelium of the trabecular wall of Schlemm's canal. The data were obtained from the grouped treated and untreated eyes and were calulated for an area of 500 000 μm^2. The figures in parentheses are conversions to an area of 11 mm^2*

	Pore conductance ($\mu l\ min^{-1}.\ mmHg^{-1}$)		*Pore resistance* ($mmHg\ min.\ \mu l^{-1}$)	
	All pores	*Pores < 3 µm*	*All pores*	*Pores < 3 µm*
Treated	0·985	0·837	1·02	1·20
	(21·7)	(18·4)	(0·0462)	(0·0543)
Untreated	0·104	—	9·61	—
	(2·29)	—	(0·437)	—

greater than 3 µm represent only 3% of the total number in the pilocarpine-treated group, they contribute 15% to the fluid conductance. The ratio between the pore resistance of the control group and the pore resistance of the pilocarpine-treated group is 9·47 when all the pores counted are included and 8·04 when only those less than 3 µm are considered. Therefore according to this mathematical approach the effect of pilocarpine was to decrease the resistance in the pores by a probable factor of 9.

In addition it can be seen from Table 3 that the resistance offered by the pore system in the untreated human eyes is 0·44 mmHg min^{-1} μl^{-1}. This value represents only one-sixth of the total trabecular resistance (3 mmHg min^{-1} μl^{-1}) as estimated by Grant (1958). These observations are in agreement with those of Bill and Svedbergh (1972), who considered that the bulk of the trabecular resistance is outside the canal endothelium and is probably in the underlying endothelial meshwork.

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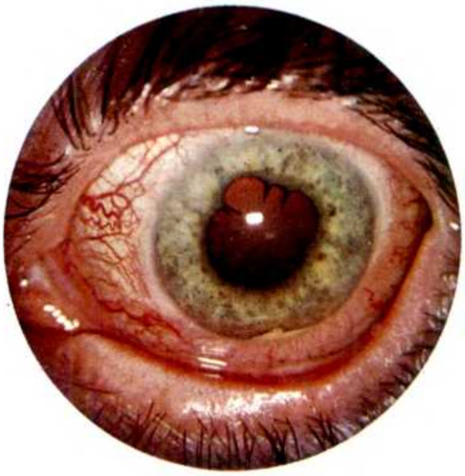

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Management of acute primary angle-closure glaucoma: a long-term follow-up of the results of peripheral iridectomy used as an initial procedure

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SUMMARY For the past 12 years peripheral iridectomy has been used as the initial surgical procedure after an acute attack of angle-closure glaucoma. The operation has been performed 2 to 5 days after the pressure has been controlled medically and has been followed routinely by prophylactic peripheral iridectomy in the fellow eye. Peripheral iridectomy for primary acute angle-closure glaucoma controlled the condition without any need for further medical or surgical therapy in 72% of cases. Careful and frequent follow-up within the first 4 postoperative months is essential to prevent further field loss, which can occur very rapidly if the pressure is not adequately controlled. If the pressure remains uncontrolled, further surgery should not be delayed. It was impossible to decide which patients would eventually need trabeculectomy when they first attended in the acute attack. Peripheral iridectomy as a prophylactic procedure was entirely effective in preventing an acute angle-closure attack in the fellow eye.

von Graefe introduced broad iridectomy as an effective operation for acute glaucoma in 1856 (von Graefe, 1857; Adler, 1929 abridged translation). He also found broad iridectomy to be useful in some forms of chronic glaucoma and in neglected cases of acute glaucoma with field loss and optic disc cupping. However, he was uncertain of its mode of action. Curran (1920, 1931) recognised that iridectomy was usually only successful in either congestive or non-congestive glaucomas if the anterior chambers were shallow. He introduced the concept of pupil and angle blockage in angle-closure glaucoma and realised that iridotomy or iridectomy allowed drainage from the posterior to the anterior chamber, thus bypassing the relative pupil blockage. Barkan (1938), following his studies with the gonioscope, clearly separated off primary angle-closure glaucoma from chronic simple glaucoma. A clear exposition of these theories and the surgical management of angle-closure glaucoma was given by Chandler (1952), in which he also described the simple, safe method of peripheral iridectomy now in almost universal use.

The method of peripheral iridectomy introduced by Curran (1920) consisted in puncturing the limbus with a Knappe needle knife and incising the iris above. This technique was much safer and led to many less complications than the von Graefe iridectomy but was still difficult to master. Barkan (1939) further modified the operation by performing a posterior sclerotomy and then injecting the anterior chamber with fluid, as well as performing multiple iridectomies. Recently there has been a return of interest in the transcorneal section, which, if performed with the operating microscope, is safe and has many advantages over the traditional subconjunctival approach (Charleux and Etienne, 1974).

Lowe (1962, 1973) conclusively showed the value of prophylactic peripheral iridectomy in preventing acute attacks.

The purpose of this study was to elucidate the outcome of peripheral iridectomy performed in all cases in which the intraocular pressure had been controlled medically after an acute attack, and in particular to discover the time of onset, the effect, and the correct management of persistently raised intraocular pressure following the treatment of the acute attack (post-iridectomy glaucoma (Forbes and Becker, 1964)).

Materials and methods

One hundred and fifty-five eyes of 83 patients (56 females, 27 males) had peripheral iridectomies performed between January 1965 and July 1976

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and were followed up until they died or until December 1976. These patients were from a local, stable, white population and only 3% were lost to follow-up. The ages of the patients ranged from 44 to 90 years (Table 1).

Eighty-one peripheral iridectomies (Table 2) were performed for primary angle-closure glaucoma (8 of these were in the other eye of patients who had bilateral attacks). One of these peripheral iridectomies had to be repeated because the iridectomy was not full-thickness.

Eleven peripheral iridectomies were performed in patients in whom an acute attack had been precipitated by mydriatics in the outpatient department (Table 3); 63 patients had prophylactic iridectomies, and in 3 of these patients the intraocular pressure was slightly raised at the time of surgery (Table 3).

Table 1 *Age of patients with primary angle-closure glaucoma*

77 patients (81 eyes)	
Age in years	*Number of patients*
41–50	1
51–60	16
61–70	22
71–80	28
> 81	10

Youngest patient, 44 years. Oldest patient, 90 years

Table 2 *Therapy for angle-closure glaucoma*

83 patients (166 eyes)	
Initial peripheral iridectomies:	155
Other initial surgical procedures: (before January 1965)	3 (three eyes)
1 iridencleisis	
1 trephine	
1 Scheie's operation	
Medical therapy alone:	8 (eight eyes)
Reason for medical therapy alone	
4 no perception of light	
1 central choroiditis 3 infirmity	

Table 3 *Reason for peripheral iridectomy*

Primary angle-closure glaucoma (includes 8 bilateral attacks)	81 eyes*
Mydriatic-induced angle-closure glaucoma	11 eyes
Prophylatic peripheral iridectomies	60 eyes
Ocular hypertension (fellow eye)	3 eyes

* All patients with acute angle-closure glaucoma had the intraocular pressure controlled with medical therapy before surgery

A patient presenting with acute angle-closure glaucoma in our clinic has the history recorded, including the duration of symptoms, especially pain, blurring, and haloes, and the presence of any precipitating factors. The visual acuity is assessed and the intraocular pressure taken. The state of the external eye, cornea, anterior chamber, iris, and lens is noted. Particular attention is paid to the presence of spiralling of the iris and glaukomflecken. If the disc can be seen it is described in detail. An attempt is made to assess the visual field in both eyes, and gonioscopy is performed after instilling glycerin 1% in the conjunctival sac.

Over the years the initial medical treatment has varied considerably but has always consisted in the frequent instillation of miotics and acetazolamide and the occasional use of osmotic agents. The present routine is to instil pilocarpine 4% every quarter hour for 2 hours and then 4 times a day; 500 mg of acetazolamide intravenously is given initially, and this is followed by 500 mg orally 3 times a day (a lesser dose is sometimes given). Osmotic agents and sedation are now rarely used. Miotics are no longer instilled in the fellow eye. Peripheral iridectomy is performed under general anaesthetic within a few days but not on the day of admission. A prophylactic peripheral iridectomy is performed as a separate procedure within the week. After operation the acetazolamide is stopped and the pupil dilated with cyclopentolate 1%. Corticosteroid drops are not given as a routine.

The follow-up of these patients is a vital part of their care. They are seen frequently in the glaucoma clinic after operation until the pressures are found to be normal and stable. The visual fields and discs are examined carefully at each visit. If there is any increase in the size of the disc cup or there is a progressive field defect, pilocarpine 4% is given 3 times a day. If control is still not gained, trabeculectomy is performed. Some patients require further medical or surgical therapy after this.

Results

Of the 81 eyes with primary angle-closure glaucoma peripheral iridectomy alone completely controlled the glaucoma in 58 eyes (72%) as judged by return to normal of the intraocular pressure and by the maintenance of the visual field. Twenty-three patients (28%) required pilocarpine therapy in addition (Table 4). This was successful in 10 patients (12%). Further surgery was required in 13 eyes (16%)

(Table 5). One eye had 2 trabeculectomies before control was achieved; the rest required miotic therapy.

Of those who had further surgery 7 had a pressure of 34 mmHg or more 1 month after the peripheral iridectomy; 4 had pressures of less than 21 mmHg at 1 month but the pressures had risen to between 22 and 50 mmHg by the fourth month. On the other hand 3 patients with tensions of 25 to 30 mmHg 1 month after operation were eventually easily controlled with pilocarpine drops alone, but only 1 patient whose pressure was at this level at 4 months could be similarly controlled. Because of infirmity 3 patients whose pressures were 44, 28, and 27 mmHg respectively 1 month after surgery have been maintained on acetazolamide permanently. In all, 13 patients required pilocarpine therapy after peripheral iridectomy or further surgery in primary acute-angle glaucoma.

Table 4 *Pilocarpine therapy following peripheral iridectomy*

Number of eyes on miotic therapy	
(*a*) after acute primary angle-closure glaucoma	23 eyes
(*b*) after mydriatic-induced angle-closure glaucoma	6 eyes
(*c*) after prophylactic iridectomy	1 eye
(*d*) after peripheral iridectomy in fellow eye with ocular hypertension	0 eyes
(*e*) after subsequent surgical procedure following peripheral iridectomy	3 eyes
(*f*) as an alternative to surgery	3 eyes

Table 5 *Time after peripheral iridectomy of further surgical procedures*

Time after peripheral iridectomy	*Control*
Within 1 month	
1 Scheie's operation	1
1 Trabeculectomy	0
1 Krasnov operation	1
Within 4 months	
4 Trabeculectomies	2
1 Trephine	1
2 Krasnov operations	0
Between 4 and 6 months	
2 Trabeculectomies	1
1 Anterior sclerotomy	1
1 Krasnov operation	1

Control is here regarded as tension less than 21 mmHg and stable field without further medication

Of the 11 peripheral iridectomies performed for mydriatic-induced angle-closure glaucoma 6 were in 3 patients who already had disc and field changes and were previously considered to have chronic simple glaucoma. These patients were already using pilocarpine drops, and this therapy was continued after the iridectomy. Neither medical nor surgical therapy was necessary in the other eyes. One patient with a prophlylactic iridectomy needed pilocarpine therapy to maintain an intraocular pressure of 21 mmHg. The 3 eyes with ocular hypertension had their tensions returned to normal by peripheral iridectomy.

The duration of the attack prior to presentation was no indication that the patient would eventually require either miotic therapy or surgery. Five patients with histories of 5 days' duration of symptoms were controlled by peripheral iridectomy alone, yet 3 patients with symptoms of 2 days only needed further surgery (Table 6). Similarly, no correlation could be found between the final result and the height of the intraocular pressure before or after medical therapy (Tables 7 and 8). Again the presence of iris atrophy, spiralling, or glaukomflecken could not be shown to be related to the need for subsequent pilocarpine therapy or surgical procedures (Tables 9 and 10).

Although no correlation could be found between the initial visual acuity and the final result, those eyes which had had an acute attack had worse vision than those which had had peripheral iridec-

Table 6 *Duration of symptoms in 65 eyes with primary angle-closure glaucoma and their subsequent glaucoma control*

	Peripheral iridectomy		*With peripheral iridectomy and pilocarpine*		*With further surgery*	
Duration	*Control*	*Non-control*	*Control*	*Non-control*	*Control*	*Non-control*
24 hours or less	20	—	5	1	—	1
2 days	5	2	1	—	3	—
3 days	7	—	1	—	—	1
4 days	3	—	—	1	—	—
5 days or more	5	1	1	3	2	2
Total	40	3	8	5	5	4

Table 7 *Initial tension in primary angle-closure glaucoma and subsequent control*

	Peripheral iridectomy		*Subsequent pilocarpine*		*Further surgery*	
Tension (mmHg)	*Control*	*Non-control*	*Control*	*Non-control*	*Control*	*Non-control*
40–50	14	2	4	1	2	2
51–60	15	2	3	—	2	1
61–70	8	—	2	1	3	1
70+	6	—	—	—	—	—

Total of 70 tensions only as 3 unrecorded in hospital and 8 given acetazolamide by general practitioner

Table 8 *Preoperative tension after medical therapy and subsequent control*

	Peripheral iridectomy		*Subsequent pilocarpine*		*Subsequent further surgery*	
Pre-op. tension (mmHg)	*Control*	*Non-control*	*Control*	*Non-control*	*Control*	*Non-control*
10 or less	15	—	—	1	1	—
11–20	20	—	9	—	4	1
21–30	4	2	—	—	—	2
31–40	2	—	—	—	—	—
> 40	3	—	—	—	1	—

Total, 64 tensions. No record for 17

Table 9 *Presence of iris atrophy and spiralling at time of presentation and subsequent control*

14 eyes out of 67 eyes examined showed atrophy or spiralling

6 controlled with peripheral iridectomy alone

4 controlled with pilocarpine subsequently

4 needed further surgery and control still not gained in 3

Table 10 *Presence of glaukomflecken at the time of presentation and subsequent control*

Glaukomflecken in 4 eyes out of 66 examined

1 controlled by peripheral iridectomy alone

2 controlled with subsequent pilocarpine

1 controlled after further surgical procedure

tomy performed as a prophylactic procedure (Table 11). Of the 68 eyes with a follow-up of at least 5 years 8 had cataract extractions, 1 being in the eye which had had a prophylactic iridectomy.

The probable causes for visual acuity of less than 6/60 at 5 to 11 years were: 3 eyes with acute angle closure of several weeks' duration and untreated, 1 of only 24 hours' duration; 3 cases of uncontrolled residual glaucoma; 2 cases of cataract; 1 case of herpes zoster ophthalmicus; and 1 case of central choroiditis. The damaging effect of post-iridectomy glaucoma was obvious by 4 months in all eyes (Table 12).

Table 11 *Visual acuities following primary acute angle-closure glaucoma (after Lowe, 1973). The 34 patients (68 eyes) with 5 to 11 years follow-up*

	Affected eye Initial operation		*Fellow eye Initial operation*	
Visual acuity	*Drainage procedure*	*Peripheral iridectomy*	*Peripheral iridectomy*	*No operation*
6/5	—	—	3	—
6/6	—	2	3	—
6/9	—	3	4	—
6/12	—	6	5	—
6/18	—	7	6	2
6/24	—	3	3	—
6/36	—	6	2	—
6/60	—	1	1	—
3/60	—	3	—	—
CF	2	—	—	1
HM	—	2	—	—
P of L	—	—	—	1
NPL	—	1	—	1

Table 12 *Time interval following peripheral iridectomy when disc cupping and glaucomatous field defects were noted (16 eyes)*

By 1 month:	10 eyes
By 4 months:	6 eyes

Discussion

Ever since von Graefe showed that broad iridectomy abolished an acute attack of angle-closure glaucoma and that useful vision often returned to that eye it has been known that this vision may be lost by chronic residual raised intraocular pressure (residual post-iridectomy glaucoma (Forbes and Becker, 1964)).

This study has confirmed that a peripheral iridectomy should be the initial surgical procedure following the termination of an acute attack with miotics and acetazolamide, 72% being completely controlled by peripheral iridectomy alone. A further 12% were controlled simply by the addition of pilocarpine. The problem has been to predict which patients will require this additional therapy or further surgery, which we found to be successful in a further 10%. This leaves 6% uncontrolled at any one time (Tables 4 and 7).

We have found that it was impossible to predict from preoperative criteria including duration of symptoms (Table 6), initial visual acuity, intraocular tensions before (Table 7) and after (Table 8) medical therapy, presence of spiralling and atrophy of the iris (Table 9), glaukomflecken of the lens (Table 10), and Goldmann gonioscopy preoperatively or at operation which patient would be left with a residual raised pressure and need further medical and/or surgical therapy.

Recognising that post-iridectomy glaucoma may occur, we have devoted much attention to predicting this on preoperative examination. The most reliable routine is to estimate the degree of angle closed by peripheral anterior synechiae, there being a direct relationship between degree of synechial closure and postoperative glaucoma (Chandler, 1952; Forbes, 1974). It is said to be possible to differentiate appositional contact from synechial closure preoperatively by indentation gonioscopy (Forbes, 1966, 1974) or operative gonioscopy (Shaffer, 1957 Unfortunately this correlation is not absolute and is, in our experience, unreliable. Furthermore these examinations cannot detect trabecular damage due to prior iris contact (Barkan, 1954).

The treatment of choice must be peripheral iridectomy with extremely careful and very frequent follow-up to determine those patients in whom the intraocular pressure is going to remain uncontrolled.

To our knowledge, no one has emphasised the remarkable speed with which the field can be lost following peripheral iridectomy after an acute attack, many eyes being severely damaged within 3 months of the acute attack if the residual glaucoma is not controlled. Readings of the early postoperative intraocular pressures alone are not sufficient to predict which eyes will be further damaged. Several patients with only slightly raised intraocular pressures developed severe field loss with extreme rapidity, and it is therefore essential to examine the visual fields and observe the optic discs at not longer than 2-weekly intervals for at least 4 months after surgery (Table 11). It seems that the disc can become excavated extremely rapidly in those patients who have not previously been subjected to prolonged moderate rises of intraocular pressure.

The intraocular pressure usually becomes stable at low levels within 4 months, but by this time the damage has been done.

If there is any evidence of visual field loss, then further surgery, preferably trabeculectomy, should be performed. Miotics alone are usually inadequate, and procrastination is dangerous (Playfair and Watson, 1978). The longer the interval between failure of control and surgery the worse the surgical results. Those eyes operated upon between 4 and 6 months later were left with very little useful field of vision even though the intraocular pressure was controlled (Table 5).

At the beginning of this investigation we were not certain which operative procedure was likely to be the most effective. For example, Scheie reported excellent results for iridectomy with scleral cautery for neglected cases of acute closed-angle glaucoma (Scheie, 1964). We now conclude that trabeculectomy is both safe and usually effective, but the operation may need to be repeated several times on the same eye. The ability to reform the anterior chamber at the end of the operation diminishes the chances of inducing malignant glaucoma. The conclusions reached over the Krasnov operation (Playfair and Watson, 1978) also apply to this group of patients. We do not consider it to have any particular advantage over trabeculectomy. We could not find any evidence that the density of cataracts increased after peripheral iridectomy.

Prophylactic iridectomy was first advocated by von Graefe for subacute attacks (von Graefe, 1857), and its value in asymptomatic fellow eyes has been particularly emphasised by Lowe (1962, 1973). We confirm this view. Only 1 of our patients required further miotic therapy after peripheral iridectomy.

We thank all the staff of the Eye Department for their help and co-operation in the collation of this material and in particular Mr J. E. Cairns and Mr J. D. Scott for their permission to include their patients in the survey. We also thank Mrs J. McCombie for typing the manuscript and the Medical Illustration Department for its help with the tables.

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Management of chronic or intermittent primary angle-closure glaucoma: a long-term follow-up of the results of peripheral iridectomy used as an initial procedure

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SUMMARY Patients presenting with either intermittent closed-angle glaucoma which gave rise to subacute congestive attacks or with chronic angle-closure glaucoma were followed up over 12 years. Peripheral iridectomy was performed as a primary procedure on these patients during this period. It was found to be a highly effective procedure in those patients without field loss at the time of presentation, but because of the figures presented here we would recommend that any patient presenting with angle closure and disc and field changes should have a trabeculectomy performed as a primary procedure. We found no way of predicting which patients would require further surgery from the history, initial intraocular pressure, or the gonioscopic findings. No patient in this series developed malignant glaucoma after trabeculectomy although it occurred in 2 eyes after peripheral iridectomy.

The management of acute closed-angle glaucoma in which the intraocular pressure rises rapidly causing corneal oedema, pain, and vomiting is not in dispute; nor is the management of the fellow eye of a patient who has had an acute attack. Peripheral iridectomy is effective. When, however, the angle of the anterior chamber is found to be closed or partially so and the intraocular pressure raised only moderately or even not at all, the management becomes more difficult and controversial (Murphy and Spaeth, 1974).

Since the introduction of gonioscopy (Barkan, 1936) it has been assumed that those patients who have closed or very shallow angles would develop angle-closure attacks. It was also assumed the raised intraocular pressure was due to the iris occluding the angle if this could be shown to be in contact or largely so when the patient first attended (Chandler, 1952). Peripheral iridectomy should therefore be the treatment of choice. This approach largely ignores the fact that if an angle has been occluded for a prolonged period secondary changes occur in the drainage mechanisms (Barkan, 1954). However, it has been shown that chronic angle-closure glaucoma may result from the closure of the filtration angle by irido-corneal contact alone (Foulds and Phillips, 1957), and it has been our custom (although not universally carried out) to treat this group of patients by peripheral iridectomy as a first procedure.

There is some evidence also that the administration of miotics to these eyes will precipitate an acute attack (Lowe, 1962; Chandler and Grant, 1962) so that rather than treat a patient with raised intraocular pressure and a closed angle with miotics they have been treated by peripheral iridectomy.

Table 1 *Sex and age distribution*

53 females with age range 43–82 years and 66% between 61 and 80 years
31 males with age range 39–83 years and 64·5% between 61 and 80 years

Materials and methods

Control was considered to have been achieved if the intraocular pressure was 21 mmHg or less, there was a stable field with 2 and 5/2000 white targets on a Bjerrum screen, and the optic disc cupping did not change.

Eighty-four patients (168 eyes) were followed up from January 1965 until December 1976. There were 53 females and 31 males. The minimum follow-up was 4 months. The population is stable and white (Table 1).

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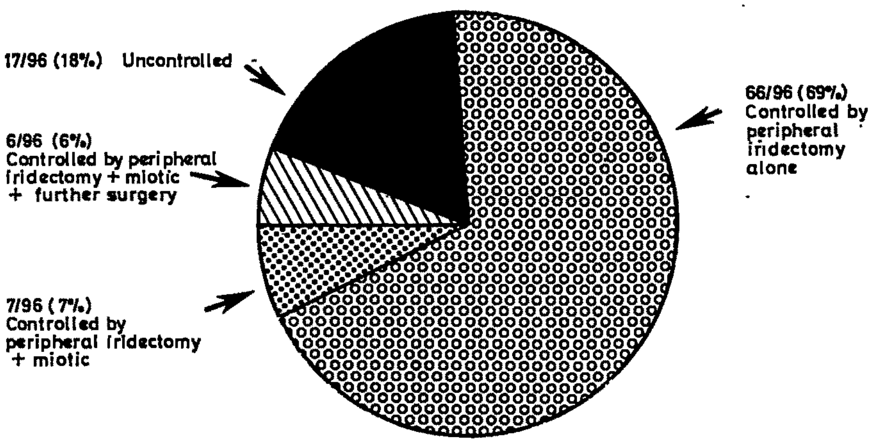
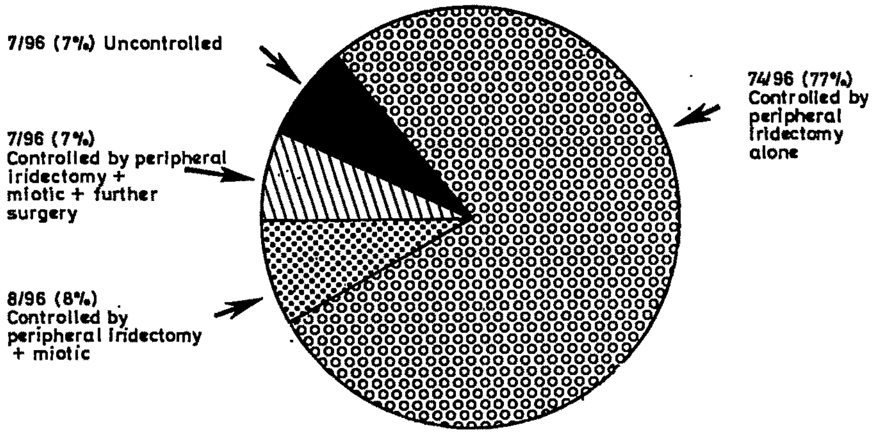
(a) Intraocular pressure control



(b) Field control



Figs. 1a,b *Control of the glaucoma as judged by intraocular pressure control* (a) *and by the visual field* (b) *in patients who had no field loss at the time of presentation*

One hundred and sixty eyes had initial operations during this period. Peripheral iridectomy was performed on 158 eyes and trabeculectomy on 2 eyes. Eight eyes were not operated upon for the reasons shown in Table 3 even though they fulfilled the criteria for surgery (Tables 2 and 3).

Table 2 *Type of operation performed*

Number of eyes with peripheral iridectomy as initial procedure	158
Number of eyes with trabeculectomy as initial procedure	2
Number of eyes not operated on during this study	8

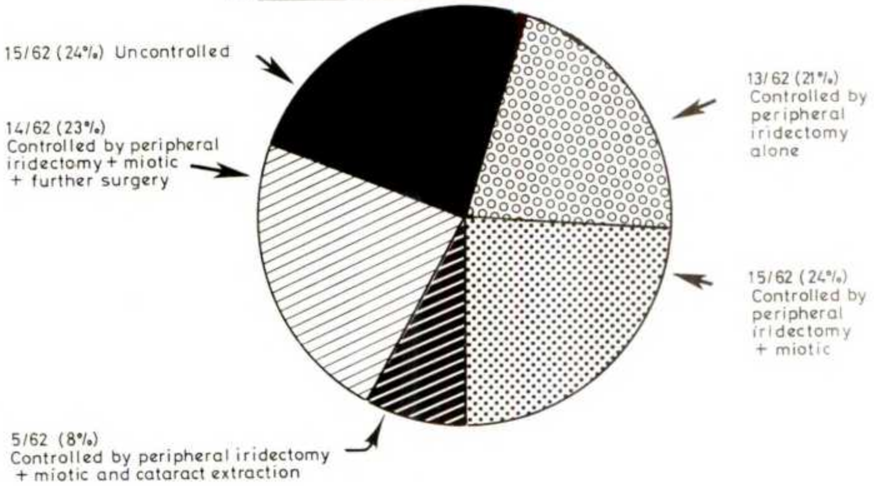
Table 3 *Reasons for not operating in 8 eyes*

6 eyes with absolute glaucoma and no perception of light (1 eye enucleated)
2 eyes with absolute glaucoma and prior anterior sclerectomy
1 eye prior to enucleation for glaucoma

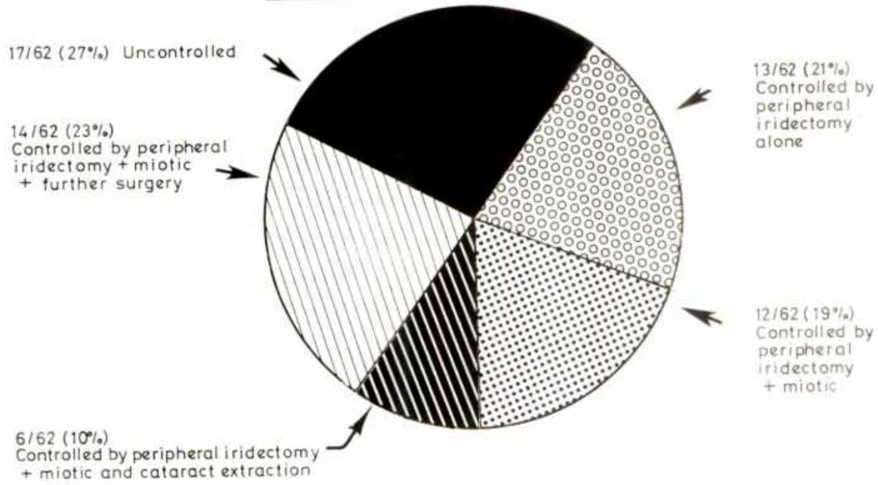
Results

The results of the various forms of therapy were analysed. The eyes were separated into 2 groups: those without field loss at presentation and those with field loss, and the degree of intraocular pressure and field control was compared (Figs. 1*a*, *b*, and 2*a*, *b*). The intraocular pressure was controlled by peripheral iridectomy alone in 69 % of those without field loss initially. In this group 77 % had no further loss of field, while only 21 % of those with field loss when first seen had their intraocular pressure controlled or did not suffer further field loss when treated by peripheral iridectomy alone. At any one time 7 % of those without field loss initially were

(a) Intraocular pressure control



(b) Field control



Figs. 2a, b *Control of the glaucoma as judged by intraocular pressure control* (a) *and the visual field* (b) *in patients who showed field loss when they first presented*

losing field, but 27% of those eyes with initial field loss were still losing field.

The results were further analysed to compare the degree of tension and field control with the findings on initial gonioscopy in those eyes without a history of congestive attacks (Table 4). The results were also analysed from those patients who had had symptoms of congestive attacks (Table 5).

Table 4 *Tension and field control versus gonioscopic assessment of angle (129 eyes)*

Gonioscopy findings	*Tension control*	*Field control*
Narrow	28/44 (64%)	30/44 (68%)
1–50% closure	9/19 (47%)	10/19 (53%)
51–99% closure	5/22 (23%)	6/22 (27%)
100% closure	14/44 (32%)	15/44 (34%)

Table 5 *Eventual control of glaucoma when compared with an initial history of congestive attacks*

Number of eyes with history of congestive episodes	29
Without initial field loss	27
Control of tension by peripheral iridectomy alone	19/27
Control of field by peripheral iridectomy alone	25/27
With initial field loss	2
Control of tension by peripheral iridectomy alone	1/2
Control of field by peripheral iridectomy alone	1/2

Of the 62 eyes with initial field loss and managed by peripheral iridectomy as an initial procedure 31 had 100% closure of the angle at initial gonioscopy. The therapy and degree of tension and field control is seen in Tables 6 and 7.

Further surgery in this series was either trabeculectomy or Krasnov's iridocycloretraction. Further surgery has been carried out after initial peripheral iridectomy in 26 eyes (Table 8). Fifteen of the further surgical operations were performed on eyes with initial field loss and 50 to 100% closure of the angle on gonioscopy. Control had still not been achieved for intraocular pressure and/or field despite further surgery and miotics in 13 eyes out of 158 eyes treated initially by peripheral iridectomy. Cataract extraction was necessary in 17 of the 158 eyes (11%) which had had peripheral iridectomies as primary procedures (Table 9).

Discussion

The patients in this study represented a heterogeneous group of glaucomas. They ranged from chronic simple glaucoma with narrow angles to classical primary chronic closed-angle glaucoma. If the diagnosis of glaucoma requires the triad of raised intraocular pressure, cupped disc, and field defect, then many patients did not have glaucoma. Be that as it may, we are faced continually with the clinical decision of what is the best management for patients with variable combinations of intraocular pressure greater than 21 mmHg and narrow through to 100% closed angles, with and without field defects.

Table 6 *Thirty-one eyes with 100% closure of anterior chamber angle on gonioscopy and a field defect at first examination and the degree of control of tension and field with therapy*

Treatment	*Control of tension*	*Control of field*
Peripheral iridectomy	6/31 (19%)	6/31 (19%)
Peripheral iridectomy +miotic	5/31 (16%)	4/31 (13%)
Peripheral iridectomy +cataract extraction	1/31 (3%)	2/21 (10%)
Peripheral iridectomy +miotic +further operation	7/31 (23%)	7/31 (23%)
Uncontrolled at any given time	12/31 (39%)	12/31 (39%)

Table 7 *Fourteen eyes with 100% closure of anterior chamber angle on gonioscopy but without a field defect at first examination and the degree of control of tension and field with therapy*

Treatment	*Control of tension*	*Control of field*
Peripheral iridectomy	8/14 (57%)	9/14 (64%)
Peripheral iridectomy +miotic	1/14 (7%)	3/14 (21%)
Peripheral iridectomy +cataract extraction	—	—
Peripheral iridectomy +miotic +further surgery	1/14 (7%)	1/14 (7%)
Uncontrolled at any given time	4/14 (29%)	1/14 (7%)

Table 8 *Further surgical procedures following peripheral iridectomy*

Krasnov's iridocycloretraction	5 eyes	
Trabeculectomy	24 eyes	
Procedure	Control of tension	Control of field
Krasnov's	2/5	2/5
Trabeculectomy	18/24 (75%)	19/24 (79%)

The three failed Krasnov operations were followed by trabeculectomy

Table 9 *Cataract extractions (17 eyes)*

	Number of extractions after peripheral iridectomy with or without miotic	*Number of extractions after further surgery*
Without initial field defect (96 eyes)	5 (29%)	—
With initial field defect (62 eyes)	10 (59%)	2 (12%)

It is generally accepted that peripheral iridectomies should be performed bilaterally if there has been a congestive attack or a history suggestive of that. Provided a careful check is made on the visual fields in the immediate postoperative period this is an entirely satisfactory procedure (Playfair and Watson, 1978). Repeated attacks of angle closure will probably cause peripheral anterior synechiae or trabecular damage and therefore make the glaucoma difficult to control. However, in this series the field was stabilised in 26 out of the 29 eyes by peripheral iridectomy alone. A history of congestive attacks was not found to be of any prognostic significance with regard to the need for further surgery.

We agree with Gelber and Anderson (1976) that the gonioscopic appearance of the angle is of little help in deciding when to perform a trabeculectomy as an initial procedure (Table 4). However, control was twice as likely if the angle was completely open as if it was completely closed. Many authors feel that there is a strong case for basing surgical decisions in closed-angle glaucoma on the degree of closure of the angle by peripheral anterior synechiae (Chandler, 1952; Shaffer, 1957; Forbes, 1974).

In those patients (and they are the majority) who have narrow to closed angles, minimal rises of tension or none at all, and who do not have field defects at the time of presentation the management is controversial. Although we might have managed these patients conservatively, we considered that peripheral iridectomy prevented further closure of the angle and damaging pressure rises (Tables 6 and 7) (Foulds and Phillips, 1957). Peripheral iridectomy will also permit the safe use of miotics if these become necessary.

The difficult patients are those who present initially with a field defect, cupped disc, variable angle closure, and raised intraocular pressure. Until now we have tended to manage these patients by performing peripheral iridectomies immediately and if control was ineffectual adding miotics, leaving further surgery until later. Peripheral iridectomy will certainly control classical chronic closed-angle glaucoma, but we have found this to be the diagnosis in only a minority of patients.

CASE REPORTS

A women was aged 71 in January 1975 when she was referred by her optician with glaucoma. She had had an amblyopic left eye (astigmatic) from childhood but had no complaints other than difficulty with reading. Her brother and sister had had glaucoma. Her visual acuities were right 6/18 (with 0·5 DS), left 6/60 (not improved with spectacles). The intraocular tensions were right and left 60 mmHg, the anterior chambers were shallow, and gonioscopy showed both angles to be 100% closed. The optic discs were grossly cupped. Bjerrum field testing showed bilateral gross arcuate scotomas. Acetazolamide 250 mg 3 times a day orally and pilocarpine 4% 3 times a day to both eyes reduced the tensions to right 22 mmHg, left 15 mmHg, and opened both angles by 5 days. Bilateral peripheral iridectomies were performed. The intraocular pressures were thereafter controlled readily with pilocarpine 2% 3 times a day. Unfortunately further surgery was frequently required (Table 8).

A woman was aged 65 in April 1974 when she went for a routine check for reading glasses. She was asymptomatic. Visual acuities were right 6/36 (plano) and left 6/7·5 (+0·75 DS). The intraocular tensions were found to be right 62 mmHg, left 60 mmHg, and the optic discs to be severely cupped. Field examination on a Bjerrum screen showed there to be a gross right glaucomatous defect preserving a central island and variable arcuate scotoma in the left eye. On Goldmann gonioscopy the right angle was 100% closed and the left 75% closed. Bilateral peripheral iridectomies were performed that week. In August 1974, despite pilocarpine 4% 3 times a day and acetazolamide 250 mg 4 times a day the intraocular tensions were right 36 mmHg, left 42 mmHg. The angles were now open. There was a suggestion of further field loss, so bilateral trabeculectomies were performed.

The intraocular pressure remained controlled until July 1976 with pilocarpine 4% eye drops 3 times a day in both eyes. By then there was increasing nuclear sclerosis and the left field defect was larger, so bilateral Krasnov iridocycloretractions were performed. Over the next 9 months there was only tenuous control with pilocarpine eye drops, and in May 1977 both cataracts were removed through corneal sections. In September 1977 the intraocular tensions were right and left 25 mmHg, visual acuities with aphakic correction right 6/12, left 6/9, and the fields showed some improvement after the cataract extractions. Further pilocarpine therapy has not been necessary.

It was hoped that Krasnov's iridocycloretraction operation (Krasnov, 1969, 1971) would be the operation of choice in this situation, but unfortunately it has not proved to be. The operation has the theoretical advantage of opening the pathway to the trabeculum, but this may already be damaged. This possibility was recognised by Krasnov himself. Also it is said to be a non-drainage procedure and hence there would be less chance of malignant glaucoma developing. However, subconjunctival drainage was noted in some of our iridocycloretractions.

Malignant glaucoma followed peripheral iridectomy in each eye of 1 male patient. He was aged 54 when first seen in May 1966 with a 5-year history of abnormal vision in the left eye and a more recent left upper field defect. Visual acuity was right 6/6, left 6/5. The intraocular pressures were right 20 mmHg, left 27 mmHg. Gonioscopy showed 90% of the left angle and 40% of the right to be closed. The left disc was atrophic. The presence of a dense left-side arcuate scotoma was confirmed.

After initial therapy to the left eye with pilocarpine and acetazolamide a peripheral iridectomy was performed in June. The iris spontaneously prolapsed and the anterior chamber was not lost. On the fifth postoperative day the anterior chamber was absent and the tension 45 mmHg. The tension was controlled over several days with cyclopentolate 1% and oral glycerol. A further attack of malignant glaucoma occurred in August which could not be controlled medically, so a left intracapsular cataract extraction with broad iridectomy was performed. The anterior vitreous was removed at the same time.

In December 1966 a right peripheral iridectomy was performed. Six weeks later the patient presented with headache, haloes, and a flat right anterior chamber with a tension of 47 mmHg. This responded to 2% atropine drops.

By June 1967 the tension in the left eye remained in the 30s despite medical therapy, and a left cyclodialysis was performed. This controlled the intraocular pressure. The left visual acuity with a contact lens was 6/18, and a left squint operation was performed for secondary divergence in October 1971.

The glaucoma remained stable for the following 3 years. In November 1974, however, the patient complained of fluctuating vision in his right eye associated with haloes and pain. The tension in this right eye remained in the 30s despite hyoscine drops 0·25% twice daily and acetazolamide. In March 1975 a right Krasnov iridocycloretraction was performed. In April 1975 he had a further episode of malignant glaucoma in this right eye which was controlled by hyoscine 0·25%.

In July 1977 the visual acuity was right 6/12, left 6/9, tensions 11 mmHg right and left, and fields unchanged over the years on hyoscine 0·25% eye drops to the right eye in the morning and pilocarpine eye drops 1% twice daily to the left eye.

This patient followed a course similar to patients described by Chandler and Grant (Chandler, 1950; Chandler and Grant, 1962).

We have performed 26 trabeculectomies by the method described either by Cairns (1968) or by Watson (1972). There have been no cases of malignant glaucoma in patients treated this way. This is similar to the experience of Gelber and Anderson (1976). Nevertheless, the fear of this complication has often delayed the decision to do further surgery. Recently we have performed trabeculectomy much more readily after an initial peripheral iridectomy if control of the glaucoma was not complete. We now feel, as do Gelber and Anderson, that trabeculectomy is the operation of choice in patients presenting with classical chronic closed-angle glaucoma even though miotics and further trabeculectomy may be needed.

Conclusions

The eyes of patients with chronic angle-closure glaucoma often present with severe damage, and aggressive therapy is indicated. It is a sobering observation (Tables 6 and 7) that, if there was 100% closure of the angle, raised tension, and a field defect when the patient first presents, 38% will remain uncontrolled after peripheral iridectomy. We now feel that almost all these patients should have had trabeculectomies initially, but unfortunately we still do not know for certain who will not be adequately treated by peripheral iridectomy. There does not seem, however, to be any disadvantage in performing trabeculectomy rather than peripheral iridectomy in patients with raised intraocular pressure and field and disc changes, and we would now advocate its use as the initial procedure. Moreover, any patient who has had peripheral iridectomy needs to be closely watched after surgery, because although control may eventually be achieved it may take several months, during which time further severe field loss may occur.

We thank all the staff of the Eye Department for their help and co-operation in the collation of this material and in particular Mr J. E. Cairns and Mr J. D. Scott for their permission to include their patients in the survey. We would also like to thank Mrs J. McCombie for typing the manuscript and the Medical Illustration Department for its help with the tables.

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Single treatment laser iridotomy

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SUMMARY A technique is described for producing an iridotomy in the treatment of closed-angle and secondary glaucoma using a single pulse from a dye laser. It was successful in 28 out of 32 eyes treated, and no significant complications were encountered.

Previous publications (Perkins and Brown, 1973; Brown, 1977) have shown that it is possible to produce a functioning iridotomy with a combination of argon and ruby lasers. This had the advantage of being an outpatient procedure, particularly useful for cases in which conventional surgery was contraindicated, but had the disadvantage that several treatments were required to achieve complete penetration of the iris. Theoretical studies (Wheeler, 1977) and animal experiments indicated that lasers with a shorter pulse, such as that from a dye laser, would produce a complete iridotomy with 1 pulse (Bass *et al.*, 1977). This method has been used on 32 eyes of 28 patients in most of whom conventional surgery was contraindicated. Four patients had both eyes treated, 1 being a case of Marfan's syndrome (Table 1).

Table 1 *Numbers of patients receiving various treatments*

Diagnosis	*One treatment*	*Two treatments*
Closed-angle glaucoma	17	4
Chronic simple glaucoma with narrow angles	7	0
Secondary glaucoma	3	0
Incomplete surgical iridectomy	1	0
Total	28	4

Table 2 *Colour of iris in treated patients*

Iris colour	*No. of eyes*
Grey	10
Blue	2
Brown	20
Total	32

Methods

Two tunable dye lasers were used: Electrophotonics Model 33 and Electrophotonics Model 43. The dyes employed to date were (1) cresyl violet, (2) rhodamine 640; both of these were in a pure methanol solution and tuned to λ 633 nm; (3) rhodamine 6G (λ 590 nm) and coumarin 102 (λ 488 nm), which were prepared initially in solution with methanol and subsequently in a methanol/water mixture of 1:1.

The maximum output of the lasers is approximately 200 mJ with a pulse duration of 1 μs, but it has been found that 60 mJ with a spot size on the iris of 250 μm diameter is adequate for most eyes, and in contrast to treatment with the ruby laser the colour of the iris is not an important factor. A grey iris can be treated as successfully as a brown iris (Table 2).

The delivery system was of our own design which incorporated slit-lamp illumination, a helium-neon laser aiming beam, safety shutters, and foot switches to activate the firing sequence. Patient and observer sit at the apparatus as for normal slit-lamp examination. No local anaesthesia has been used.

The patient sees a bright flash of light and has the sensation of something striking the eye, which often causes a reflex withdrawal of the head from the headrest. No lasting pain results, but there is a temporary blurring of vision due to pigment dispersal into the aqueous. Examination immediately after lasering shows in successful cases an iridotomy varying in size from a narrow slit to a hole comparable with that produced by a surgical peripheral iridectomy. A stream of pigment particles flows into the anterior chamber, and there is immediate flattening of any iris bombé present. A fine stream of blood from the edge of the iridotomy can be seen in some eyes, but no visible hyphaema has resulted so far.

A transient rise in intraocular pressure is usual after treatment, and prednisolone 0·3% drops 4 times

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daily are prescribed for 1 week in addition to any medical treatment being used.

Results

Thirty-two eyes have now been treated, and in 28 a successful iridotomy was achieved with 1 treatment (Table 1). In the 4 eyes in which it was necessary to repeat the treatment at another site 1 week later failure of the first treatment was due to fluctuation in the power output of the laser, so that the output energy was below the predicted level.

The indications for laser iridotomy are the same as those for surgical iridectomy, and the majority of cases treated have had closed-angle glaucoma. It has, however, been found useful for cases of chronic simple glaucoma with narrow angles before the use of sympathomimetic drugs to control the tension. Laser treatment has the advantage in such cases in that it does not cause any conjunctival scarring, so that any subsequent drainage operation which may be required is facilitated.

Laser iridotomy is particularly suitable for cases in which conventional surgery is contraindicated because of the patient's general condition or any local ocular conditions (as in Marfan's syndrome with subluxated lenses or active uveitis with iris bombé).

COMPLICATIONS

No corneal lesions were observed when dyes lasing in the red-yellow band of the spectrum were used, but small epithelial lesions were seen in 2 patients when coumarin 102, which emits in the blue at λ 488 nm, was used. No lens changes have been observed, and no retinal burns or haemorrhages have been detected. One patient whose tension was 36 mmHg at the time of treatment developed minimal macular oedema a few days after treatment when the tension had dropped to 16 mmHg. The oedema resolved in 3 weeks, with recovery of normal vision.

Discussion

These results show that an iridotomy can be achieved with a single pulse from a dye laser and that this is a practical outpatient procedure with minimal disturbance to the patient. In only 4 out of 32 eyes was a second treatment necessary, and this was due to a temporary failure of the laser to emit the required energy. No significant complications have been encountered, and although the follow-up period has been short (from 1 year to 3 months) serious complications such as lens changes or retinal burns would have become obvious soon after treatment.

Our present results suggest that the wavelength of the emitted laser light is less important than the short pulse produced by the dye laser. As small epithelial lesions were produced by the blue light from coumarin 102, and light of this wavelength is scattered more by an arcus senilis, use of this dye has been discontinued. Rhodamine 6G has the advantage of a longer life (several weeks) and seems to be the most suitable dye of those used so far. Other types of laser would probably be as effective provided they produced a pulse of a similar duration to that of a dye laser.

The apparatus in use at present is not ideal for routine clinical purposes, mainly because there is no flexible coupling between the laser and the microscope, and fine adjustment of the position of the beam has to be done by moving the patient rather than the microscope. This is a technical problem which still has to be solved in order to design a system suitable for routine clinical use.

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Acute aphakic pupil block glaucoma: an alternative surgical approach

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SUMMARY In a series of 7 cases of acute aphakic pupil block glaucoma a surgical approach designed to break adhesions between the iris and the anterior hyaloid face was uniformly successful. Reasons for the success of the method are discussed and comparisons made with other surgical approaches.

Acute aphakic pupil block glaucoma is a relatively uncommon condition characterised by ocular hypertension, shallowing of the anterior chamber, and marked anterior convexity of the iris together with angle closure (Figs. 1 and 2). It can develop at any time in the first few weeks after cataract extraction. The hyaloid face may be *intact*, protruding into the anterior chamber, and, less frequently nowadays, *broken* and prolapsing through a posterior capsulotomy. In both instances, vitreoendothelial contact is the rule, the glaucoma being complicated by corneal endothelial decompensation. Recognition of the condition prompts immediate treatment with

1

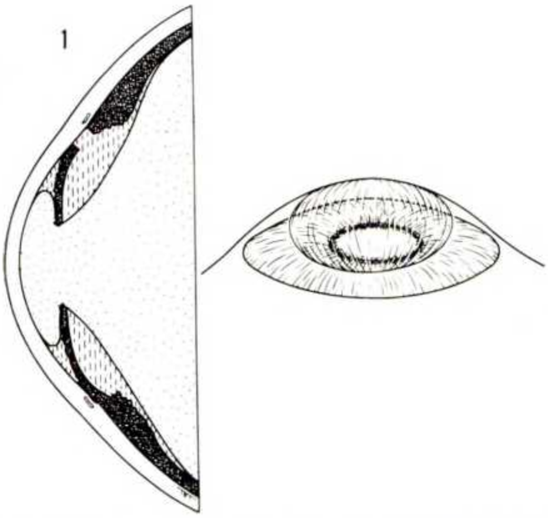
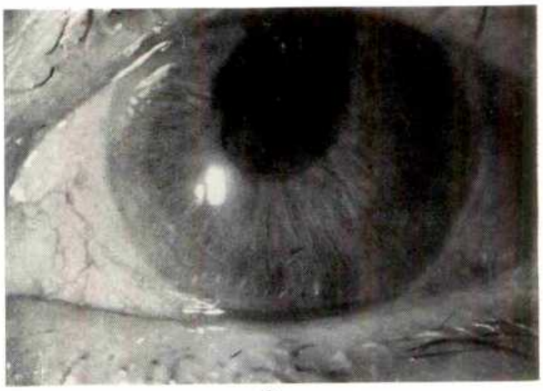
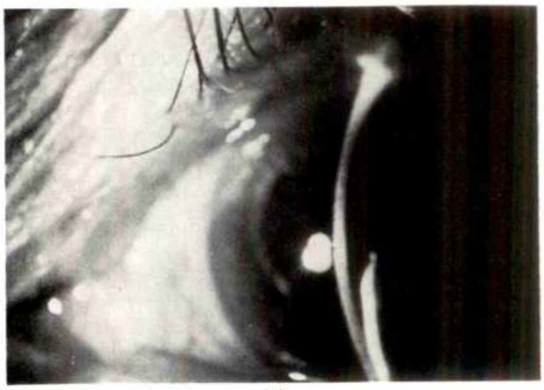


Fig. 1 *Cross-section and diagrammatic three-dimensional view indicating relationships between vitreous, aqueous, and iris in aphakic pupil block. It should be noted that the plan of iridovitreal contact drawn is only one of the three theoretical possibilities (see text)*



2a



2b

Figs. 2a and b *Diffuse and slit illumination of an eye of Patient 4 with aphakic pupil block*

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mydriatics, carbonic anhydrase inhibitors, and hyperosmotic agents in an attempt to break the pupil block. Mydriasis may not be achieved if the intraocular pressure is too high or the anterior chamber flat. Even if mydriasis is achieved in those eyes with an intact anterior hyaloid, iridovitreal adhesion may persist with tightening the anterior hyaloid, so that despite deepening of the anterior chamber the pupil block persists.

Failure to obtain rapid cure with medical treatment is an indication for surgical intervention in the hope of preventing both irreversible damage to the optic nerve as well as chronic aphakic angle closure glaucoma. This paper is concerned with the surgical cure of aphakic pupil block in eyes with an intact anterior hyaloid and will describe an alternative surgical approach to those techniques promulgated at present.

Many surgical techniques have been described for relieving this condition. They can be divided into operations based on *(a)* the concept of aqueous pooling behind the iris and in front of the anterior hyaloid, the operations including iridotomy (Bowman, 1863), needling (Smith, 1891), iridectomy (Knapp, 1895; Weeks, 1923; and others), and argon laser iridotomy (Anderson *et al.*, 1975; Patti and Cinotti, 1975); and *(b)* the concept of intra- or retrovitreal pooling of aqueous, the operations including incision of the anterior hyaloid face (Shaffer, 1954; Wright, 1968) and vitreous aspiration with and without iridectomy (Shaffer, 1954; Chandler, 1954; Meisekothen and Allen, 1968; and others). The very multiplicity of surgical approaches suggests that none is ideal. This paper describes a simple surgical approach, found to be effective in 7 successive cases of aphakic pupil block glaucoma. Simplicity together with a successful surgical result suggests that this technique should be tried first in the surgical treatment of acute aphakic pupil block.

Operative technique

The operation aims to re-establish communication between the posterior and anterior chambers by separating iris from anterior hyaloid with a Castroviejo iris repositor (chosen because the long narrow blade facilitates delicate manipulations within the anterior chamber).

Under local or general anaesthesia the eye is fixed at the limbus by means of fine-toothed forceps. A transcorneal paracentesis just anterior to the site of fixation is performed with a Bowman knife. As the anterior chamber is, at best, extremely shallow, the knife track has to be a very shelving one.

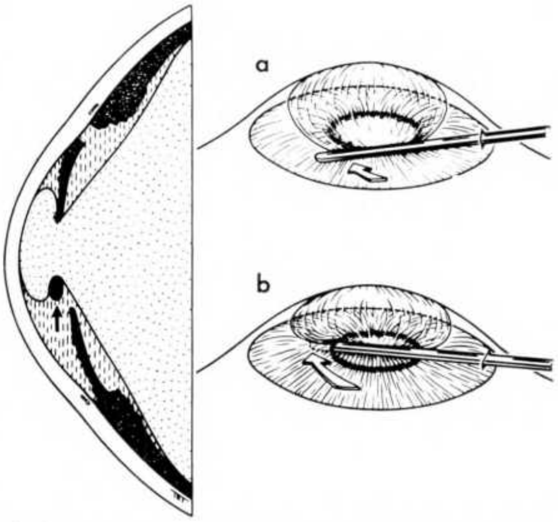


Fig. 3 *Cross-section and diagrammatic three-dimensional view illustrating the 'sweep' action of the iris repositor. In the cross-section the repositor is shown breaking the pupil block by stretching anterior hyaloid face, (black arrow). In the three-dimensional views the iris repositor (white arrow) is shown lying in front (a), and behind (b) the iris plane while separating iris from anterior hyaloid*

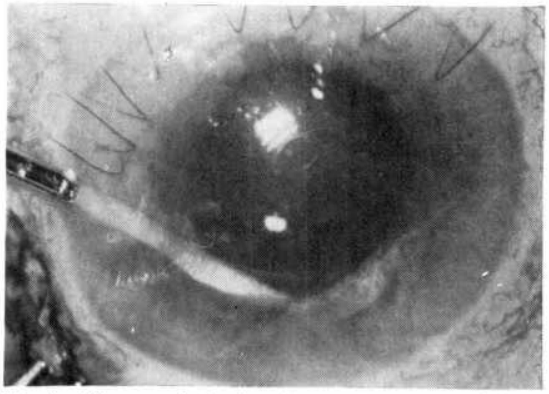


Fig. 4 *Photograph showing iris repositor passing behind the iris*

The Castroviejo repositor is introduced into the anterior chamber, gently displacing the convex iris surface posteriorly so as to avoid contact with the corneal endothelium. The repositor is directed above or, more usually, below the pupil margin so as to lie between the anterior iris surface and the protruding vitreous face (Figs. 3 and 4). Care must be taken not to perforate the anterior vitreous face with the blunt end of the repositor. Sufficient length of the repositor is introduced into the anterior chamber to enable the tip to reach that part of the

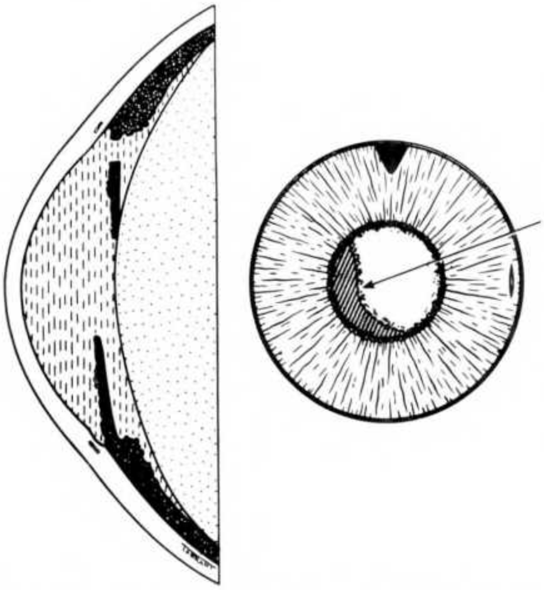
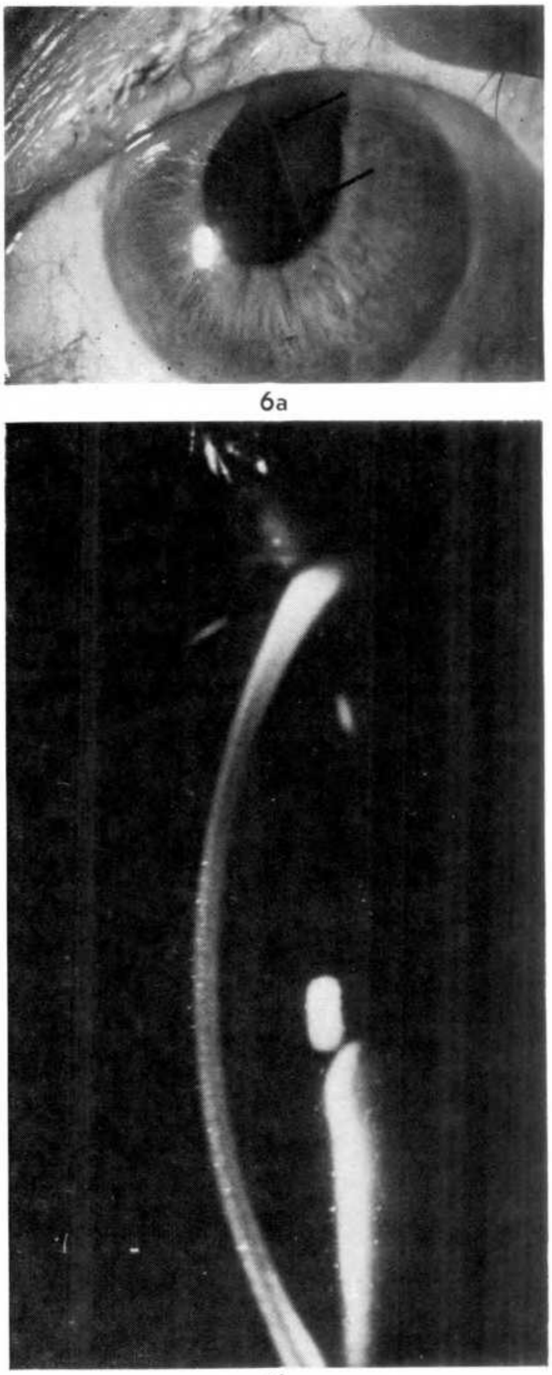


Fig. 5 *Diagrammatic cross-section and external view after successfully treating aphakic pupil block. The cross-sectional diagram shows a deep anterior chamber having free communication with the posterior chamber. The external view demonstrates the occasional line of pigment on the anterior hyaloid surface indicating the line of iridovitreal adhesion (arrow)*

pupil farthest away from the paracentesis site. The shaft of the repositor is swept towards the pupil, pushing the anterior hyaloid face before it. This action stretches the anterior hyaloid and in some cases is sufficient to slide the vitreous face from behind the iris, breaking any iridovitreal adhesions.

Immediate deepening of the anterior chamber indicates that communication between anterior and posterior chambers has been re-established. Whether or not the anterior chamber has deepened, the tip of the repositor is introduced through the pupil close to the pupil margin and passed between iris and anterior hyaloid. The repositor may now be swept along the pupil margin for close to 180° separating the iris from the anterior hyaloid face. In the 7 cases reported here these 2 manoeuvres successfully broke the pupil block, shown in each case by *spontaneous* deepening of the anterior chamber (Figs. 5 and 6). It should be emphasised that, although the pupil block has been broken, the subsequent intraocular pressure depends on the extent to which the angle of the anterior chamber was occluded or damaged before the operation.

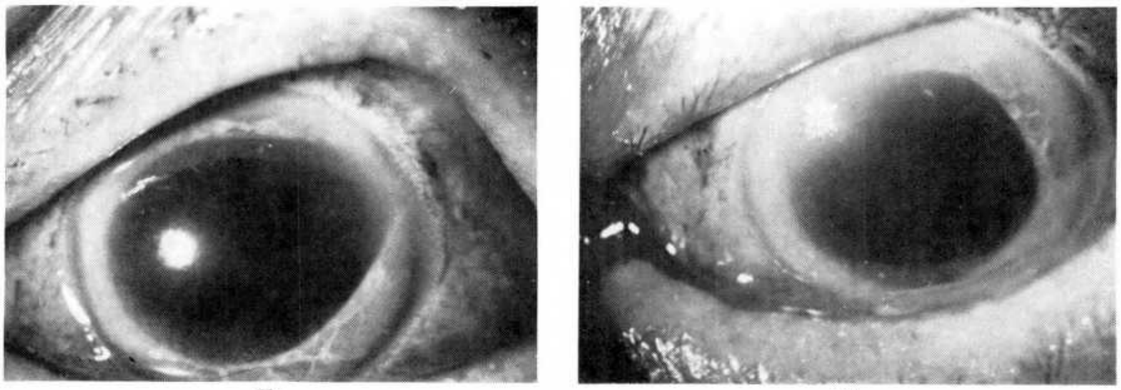
Three eyes in this series had developed iris prolapse by the time they were operated upon. In each case it was possible to 'hook' the repositor through



6a

6b

Figs. 6a and b *Photographs of Patient 4 after successfully breaking the pupil block illustrating the deep anterior chamber together with a pigmented line on the anterior hyaloid face (arrow)*


7a 7b

Figs. 7a and b *Photographs of Patient 3 before operation with an iris prolapse, and postoperatively after the iris had been pulled back into the anterior chamber*

the iridectomy and pull the iris away from and out of the section. No repair of the section was required (Fig. 7). In the other eyes after the anterior chamber had deepened it became apparent that the vitreous face was still occluding the iridectomy. It was possible to pass the iris repositor through the iridectomy and stretch the aperture sufficiently to break the iridovitreal adhesion.

Results

These have been summarised in Table 1. Patients 1 and 2 each had an unsuccessful incision of the anterior hyaloid face and anterior vitreous before the iridovitreal adhesions were divided. Patient 3 had persistent ocular hypertension despite a deep anterior chamber and required a further operation for glaucoma within the first month. No eye suffered visible corneal endothelial decompensation with corneal oedema. In Patients 1 and 2 the incised anterior hyaloid face reformed, and at 1 month only 1 eye had a persistently broken anterior vitreous face. In a number of eyes a line of pigment on the anterior hyaloid face indicated a line of pupillo-vitreal adhesions (Figs. 5 and 6).

Discussion

It is convenient to divide the discussion into 3 sections: the location of retroiridic aqueous, the

Table 1 *Aphakic pupil block—results*

Patient	*Time between cataract extraction and diagnosis of pupil block*	*IOP*	*Surgical approach*	*One month post operation for aphakic pupil block*		
				IOP	*Anterior hyaloid face*	*Anterior chamber depth*
1	1 week	45	Incision anterior hyaloid then division posterior synechiae. Repositor used to pull iris out of section	18	Intact	Deep
2	2 weeks	40	Incision of anterior hyaloid first, then division posterior synechiae	15	Intact	Deep
3	1 day	35	Division posterior synechiae. Repositor used to pull iris from section	14*	Intact	Deep
4	1 week	30	Division posterior synechiae	21	Intact	Deep
5	2 days	42	Division posterior synechiae	18	Intact	Deep
6	2 days	35	Division posterior synechiae	15	Intact	Deep
7	2 days	45	Division posterior synechiae with rupture anterior hyaloid	10	Broken	Deep

*Further glaucoma surgery was required 3 days later despite cure of the pupil block because of residual peripheral anterior synechiae surgical technique, and possible retro- and intravitreal pooling of aqueous.

LOCATION OF RETROIRIDIC AQUEOUS

The iris may have aqueous, aqueous and vitreous gel, and solely vitreous gel in contact with the posterior iris surface (Shaffer, 1954; Chandler, 1954; Weiss and Shaffer, 1972; Anderson *et al.*, 1975). In the first instance pupillovitreal adhesions, in the absence of a patent iridectomy, are the cause of the block. Examples of this have been demonstrated on histological sections by Smith (1891), Hudson (1912), Shaffer (1954), and others. These eyes may or may not have extensive inflammatory exudate within the anterior chamber (Chandler and Johnson, 1947).

Adhesions between the posterior iris surface and the anterior hyaloid face have been cited as reason for the failure of an iridectomy (Kolker and Hetherington, 1976) or laser iridotomy (Anderson *et al.*, 1975) to break the block at one site but not at another.

If it were possible to identify those parts of the iris with aqueous behind them, iridectomy would be a reasonable and certainly curative procedure. Kolker and Hetherington (1976) note, however, that iridectomy under these conditions is a 'formidable' procedure, and certainly the thought of performing an iridectomy in a hypertensive aphakic eye in which vitreous may lie immediately behind the iris is not obviously attractive. Kolker and Hetherington (1976) suggest looking through the pupil for an 'optically clear zone' within the anterior vitreous that may be a pocket of aqueous, and performing an iridectomy at that site. In the author's experience, however, persistent corneal stromal oedema in many eyes prevented a sufficiently clear view of the anterior vitreous to observe such optically clear zones.

Ultrasound scanning might show an interface between aqueous pool and the retrodisplaced anterior hyaloid. B-scan ultrasound was performed for 2 of the eyes, but such an interface could not be seen. In 1 eye not reported here, which had aphakic pupil block for at least 2 months, an acoustically clear zone behind the iris could be seen (McLeod, personal communication). Failure to visualise such acoustically clear zones in 2 eyes reported here only reflected the ultrasound being obtained soon after onset of the block, when the aqueous pool is presumably much smaller. Buschman and Linnert (1976), however, reported echo-free areas within the vitreous cavity in eyes with aphakic pupil block and suggested that these regions were pockets of aqueous. But differentiation by ultrasound between intravitreal aqueous and areas of vitreous gel collapse may well be impossible.

There would not appear to be a certain method of establishing whether aqueous or vitreous is behind any part of the iris. The problem of where to place the iridectomy was overcome by Anderson *et al.* (1975), who noted that if one (full thickness) laser iridotomy failed to break the block a second (and presumably a third) site could be chosen. Anderson *et al.* noted, however, that dark coloured irides required much more energy to produce an iridotomy, and that they could not produce one in every eye to be treated. The energy required to obtain an iridotomy with the argon laser might result in damage to other intraocular structures (Wheeler, 1977). The dye laser delivers less energy while producing an iridotomy, and so might perhaps be an ideal treatment for this condition (Perkins, personal communication).

A major advantage of retroiridic sweeping with a Castroviejo spatula is that at least 120° of the iris may be treated, and by breaking down possible iridovitreal adhesions over this area the operation has a far greater chance of establishing communication between the anterior and posterior chambers than an iridectomy or an iridotomy.

SURGICAL TECHNIQUE

This method of dividing pupillovitreal adhesions is not new, being first suggested to the author by P. Spaeth (personal communication). Christensen (1967) suggested another method of breaking the pupil block when he noted the success of passing an iris repositor through an iridectomy, behind the iris and then through the pupil, to break pupillovitreal adhesions in eyes with excessive inflammatory exudate in the anterior chamber.

The major advantages of this technique are speed and simplicity. No special precautions need be taken. The preoperative intraocular pressure should be low enough for the cornea to remain clear. In fact an intraocular pressure greater than 21 mmHg facilitates paracentesis.

The shallow anterior chamber requires a very shelving paracentesis track. The shelving nature of the track ensures that it acts as a valve, collapsing to prevent iris prolapse when the knife is withdrawn before inserting the iris repositor.

It is essential to be able to delineate the extent of the protruding vitreous face so that the Castroviejo repositor is positioned between the vitreous face and the iris surface. Care has to be taken not to push the iris repositor through the anterior hyaloid face before passing it behind the pupil. Should this occur, it is difficult to exert traction on the anterior hyaloid face and break the posterior synechiae. Furthermore when the tip of the spatula is pushed behind the iris it will remain within the vitreous gel and fail to establish a communication between the posterior and anterior chambers.

In those eyes in which sweeping the anterior hyaloid face is sufficient to break pupillovitreal adhesions, and thus break the pupil block, the vitreous face retracts and the anterior chamber deepens. Under these conditions the operator can be reasonably sure that the iris repositor passes between the pupil margin and the anterior hyaloid face. When this initial manoeuvre is insufficient, the operator cannot be sure that the iris repositor does not perforate the anterior hyaloid. (If it does, to cure the block the repositor must reperforate the face to gain entry into the aqueous pool formed around the ciliary processes. Unless this occurs, the aqueous cannot gain entry into the anterior chamber and the vitreous gel will not retract.)

The appearance of the vitreous face after cure of the pupil block allows differentiation between transfixing the vitreous gel and dividing the posterior synechiae. In the former condition aqueous will gain entry into the anterior chamber through the broken vitreous face, the break will remain, and, commonly, vitreous 'tags' will float into the anterior chamber, indicating the forward flow of aqueous. With division of posterior synechiae the vitreous face remains intact.

In this series the vitreous face was formed the day after operation in all but 1 eye, suggesting that aqueous drained into the anterior chamber *around* and not *through* the vitreous gel, and that cure of the pupil block followed division of posterior synechiae.

A sudden deepening of the anterior chamber indicated successful re-establishing of communication between anterior and posterior chamber. This useful end point *removes the need* for deepening of the anterior chamber with either air or saline—but see Jones (1968), Kolker and Hetherington (1976), and Jaffe (1976). The reason for the sudden reformation of the chamber is not clear. What may happen is that vitreous gel 'plugs' the pupil (and any iridectomy), and then as aqueous leaves the anterior chamber the gel is pushed forward by aqueous trapped in the posterior chamber. The gel structure remains attached at the vitreous base, however, and when the iris repositor deforms the plug its size is reduced so that the stretched collagen fibrils within the vitreous gel regain their normal length by retracting into the posterior segment. The dilator muscle of the iris is stretched by the bowing forwards of the iris into the anterior chamber. When the vitreous plug retracts, the iris dilator muscle contracts, removing the anterior convexity. Aqueous flows forward passively to fill the space created between iris and cornea, thus reforming the anterior chamber.

As soon as the anterior chamber does deepen, the iris repositor may be withdrawn. No corneal sutures are necessary. Topical steroid and cycloplegics are instilled.

Two of the eyes in this series suffered partial iris prolapse secondary to wound dehiscence under high pressure. In some eyes (not reported here) failure to diagnose aphakic pupil block has in the author's experience caused sufficient of the iris to prolapse to break the block, causing spontaneous deepening of the anterior chamber. For the 2 eyes in this series with iris prolapse, after the block had been broken the iris repositor was hooked around an adjacent iridectomy and used to pull the iris back into the eye. In each case, the wound was considered adequately sutured and no further action to repair it was required.

The pupil block has not been broken until the anterior chamber deepens. If retroiridic sweeping fails to break the block, it would be reasonable to diagnose 'ciliovitreal block' (Weiss and Shaffer, 1972) and search for intra- or retrovitreal aqueous.

INTRA- AND RETROVITREAL POOLING OF AQUEOUS

The concept of aqueous migrating posteriorly into the vitreous gel and eventually into the retrohyaloid space arose from *(a)* the occasional failure of an iridectomy to cure the condition, and *(b)* the success of incising the anterior hyaloid face in eyes with aphakic pupil block.

Incision of the anterior hyaloid face is not entirely satisfactory. It was recommended by Chandler and Johnson (1947) to remove obstruction to aqueous flow caused by an inflammatory membrane occluding the pupil. Shaffer (1954) suggested incision of the anterior hyaloid face even without an obvious inflammatory membrane, noting, however, that simple incision was not always enough to break the pupil block. Similar doubts about the efficacy of incising the anterior hyaloid face were expressed by Kolker and Hetherington (1976) and Jaffe (1976), all 4 authors recommending aspiration of retrovitreal aqueous.

One reason for the failures seen with incising the anterior hyaloid face was evident in Patients 1 and 2 in this series. In both cases initial incision failed to break the pupil block, which was, however, broken by retroiridic sweeping. An important point is that the anterior hyaloid face subsequently reformed, this suggesting that retroiridic pooling of aqueous, only, had occurred. This preferential location for the aqueous pool would explain failures seen with incision of the hyaloid face, for unless the block had been present for a long time, with collection of a large volume of aqueous, the essentially posteriorly directed stroke of the instrument used to incise the face would not enter the aqueous pool.

Conclusion

The eyes with aphakic pupil block glaucoma presented in this paper were cured on re-establishing communication between the posterior and anterior chambers by retroiridic 'sweeping' with a Castroviejo iris repositor. The ease and simplicity of the manoeuvre suggest that it should be tried first in all cases of aphakic pupil block when retroiridic pooling of aqueous is suspected.

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Trabeculotomy in late onset congenital glaucoma

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SUMMARY All eyes of children above the age of 1 year referred because of glaucoma were treated with trabeculotomy as the primary procedure. The surgery was modified by the excision of a rectangle of tissue in the deep scleral bed under the scleral flap instead of the classical radial incision. This serves to exteriorise Schlemm's canal while thinning the scleral tissue, without, however, entering the anterior chamber. A total of 7 eyes in 5 children between the ages of 1 and 9 years were operated upon. In 6 of the 7 eyes intraocular pressure has remained under 20 mmHg without treatment after follow-up of between 18 months and 4 years. In the seventh eye intraocular pressure was controlled for 2 years but has since required epinephrine drops twice daily for the maintenance of pressure below 20 mmHg. In 4 of the 7 eyes flat, diffuse conjunctival filtering blebs are present, but no complications have been encountered. We consider that trabeculotomy may be recommended for children with late-onset congenital glaucoma.

Trabeculotomy has been reported to be a safe, effective procedure for congenital glaucoma (McPherson, 1973), but has been less successful in adult chronic simple glaucoma (Luntz and Livingston, 1977). We wish to report a series of children with late-onset congenital glaucoma first presenting above the age of 1 year and undergoing trabeculotomy as their primary and only procedure. In 7 eyes of 5 children the surgery lowered the intraocular pressure to under 20 mmHg after a follow-up period of between 18 months and 4 years.

Materials and methods

All children above the age of 1 year referred to the eye clinic because of raised intraocular pressure were included in the study. When medical treatment was unsuccessful or inappropriate, trabeculotomy *ab externo* was performed as the primary procedure.

Initial intraocular pressures were measured with an applanation tonometer either at the slit lamp for older children or under halothane anaesthesia in younger children. In the latter cases measurements of postoperative pressures were followed by ketamine anaesthesia. Gonioscopy was performed in all patients pre- and postoperatively.

The surgical technique used was a modified form of Harms and Danheim's original method (Harms and Danheim, 1970). A limbal based conjunctival flap is dissected to expose the desired surgical area. A 4×4 mm lamellar scleral flap hinged on the corneal side is then reflected. At the anterior portion of the exposed scleral bed an additional 2×2 mm of tissue is excised, care being taken not to enter the anterior chamber. This serves to exteriorise Schlemm's canal while allowing better identification of the anatomical landmarks in the area and facilitating entry into the canal with the trabeculotome of Harms. The scleral flap is closed with two 7–0 silk sutures, and the conjunctival flap securely closed with 7–0 continuous silk sutures.

A total of 7 eyes in 5 children were operated upon and followed-up for a minimum of 18 months.

Results

A summary is given in Table 1. In all children the intraocular pressure was lowered to below 20 mmHg. In Case 5 the pressure was normal for 2 years but has subsequently required twice-daily epinephrine 1% drops to maintain this control. Four of the 7 eyes had flat, diffuse, filtering blebs; their occurrence could not be correlated with the level of intraocular pressure.

Gonioscopy preoperatively showed what appeared to be sheets of brownish mesoderm of the iris spreading over the ciliary body and trabecular meshwork. Postoperatively a widely clefted trabecular meshwork could be seen in the operated area

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Table 1 *Results of trabeculotomy for late onset congenital glaucoma*

Case	*Eye*	*Age at surgery (years)*	*Pressure before surgery*	*Final pressure*	*Bleb*	*Follow-up (years)*
1	OD	1	40	18	No	1½
2	OD	1	35	12	No	4
3	OD	3	40	10	Yes	2½
	OS	3	35	17	No	2½
4	OD	7	35	19	Yes	2
	OS	7	30	18	Yes	2
5	OS	9	31	18*	Yes	4

*Medical treatment

of the angle. Reflux of blood from the ruptured canal of Schlemm into the anterior chamber was seen in 5 of the 7 eyes.

There were no serious complications. A small hyphaema was present at the end of surgery in all eyes. There was no loss of the anterior chamber at operation in any case. In 1 eye the anterior chamber was shallow postoperatively for 1 week but spontaneously deepened. There have been no postoperative infections of the filtering blebs.

Discussion

Trabeculotomy, first described by Smith (1960), has been used in an attempt to remove the resistance to aqueous flow across the trabecular meshwork. Its success in adult glaucoma has been limited in comparison to other procedures, but it has been found to be of distinct benefit in congenital glaucoma, working just as well in eyes with cloudy corneas as in those with clear ones (Lunz and Livingstone, 1977).

80% of congenital glaucomas are apparent before the age of 1 year (Kolker and Hetherington, 1976). Those cases appearing after this age have variously been classified as infantile or juvenile glaucomas. Our experience justifies their being considered cases of late-onset congenital glaucoma, both because of their gonioscopic appearance and because of their response to treatment. Our excellent results in this series with trabeculotomy as the sole surgical procedure support this view.

We consider that accurate localisation of Schlemm's canal, the key to successful external trabeculotomy, may be made easier by excision of the deep rectangle of scleral tissue, as in our modified procedure. The thinning of the scleral flap may also aid transscleral filtration, as has recently been suggested by *in-vitro* studies (Shields *et al.*, 1977). On the other hand this thinning of the tissue may have been responsible for our high incidence of filtering conjunctival blebs. The procedure was found to be free of complications, unlike the series reported by Brachet *et al.* (1972), and the diffuse, shallow blebs have not been responsible for any postoperative infections.

Because of our success in these cases, without complications, we feel that external trabeculotomy can be recommended for children with congenital glaucoma both of early and of late onset.

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Rieger's syndrome with pericentric inversion of chromosome 6

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SUMMARY Pericentric inversion of chromosome 6 (6p+q−) was found in a girl with Rieger's syndrome and in her father. The only ocular signs in the father were prominent iris mounds and Schwalbe's line. The association of chromosomal anomalies with Rieger's syndrome indicates the need for a chromosome banding test in familial or sporadic patients with the syndrome and in patients with mild anomalies of the anterior chamber angle.

Rieger's syndrome is characterised by mesodermal anomalies of the anterior chamber angle and facial, dental, and musculoskeletal malformations. Major ocular abnormalities include hypoplasia of the anterior iris stroma, a prominent Schwalbe's line (posterior embryotoxon), and large peripheral anterior synechiae stretching from the peripheral and mid portions of the iris (Waring *et al.*, 1975). Abnormalities of the iris such as polycoria and dyscoria and secondary corneal anomalies such as microcornea and macrocornea occur frequently (Waring *et al.*, 1975). On the basis of an extensive review of 175 patients Alkemade (1969) concluded that Rieger's anomaly is inherited in an autosomal dominant pattern in 70% of cases, while 30% are thought to arise as isolated events (Alkemade, 1969). Thus, spontaneous or transmitted mutations associated with chromosomal anomalies may occur in Rieger's syndrome.

Tabbara *et al.* (1973) reported the case of a young man with Rieger's syndrome associated with an extra metacentric chromosome. A case of Rieger's syndrome with associated inverted chromosome 6 in a young girl is presented here. Similar chromosomal anomalies were found in the father, who presented minimal mesodermal anomalies of the anterior chamber angle.

Case report

CASE 1

The proposita is a 10-year-old white girl who is the product of a 38-week gestation and uncomplicated vaginal delivery. The birth weight was 3·335 kg. The only physical abnormality noted during the initial physical examination was epithelisation of the umbilicus. Soon after her birth hypoplastic upper gums were noted as well as a short lingual frenulum. She underwent frenulectomy at the age of 4 months.

The patient sat at 7 months of age and walked at 14 months despite bilateral tibial distortion (*genu varus*) which necessitated the wearing of a night brace for a brief period. She began to talk at 18 months. The child's height and weight were consistently within the 5th and 15th percentiles, and she was evaluated for the possible presence of a growth hormone disturbance. Post-exercise levels of human growth hormone were 9 ng/ml, near the lower limit of normal. Radiological appearances of the sella turcica were within normal limits. Bone age measurements using the standards of Greulick and Pyle showed no evidence for retarded skeletal maturation.

Her dentition has been markedly abnormal. At age 6 months she was found to have hypoplasia of the maxilla. Mandibular incisors appeared at 7 months of age. Recent dental films disclosed no permanent teeth except for 6-year molars.

At 5 months of age unusually shaped pupils were noted. Eye examination revealed microcornea and diagonal pupils bilaterally. Phenylephrine 2·5% eye drops were prescribed for pupillary dilatation, but therapy was unsuccessful. An examination at 16 months of age showed intraocular pressures of 16 mmHg bilaterally, and corneal diameters of 9·5 mm (horizontal) by 9·5 mm (vertical) in the right eye and 9·0 mm (horizontal) by 9·5 mm (vertical) in the left. When the child was 2½ years of age she was found to have an abnormally thickened and centrally displaced ridge of Schwalbe's line as well as numerous iris processes attached anteriorly to

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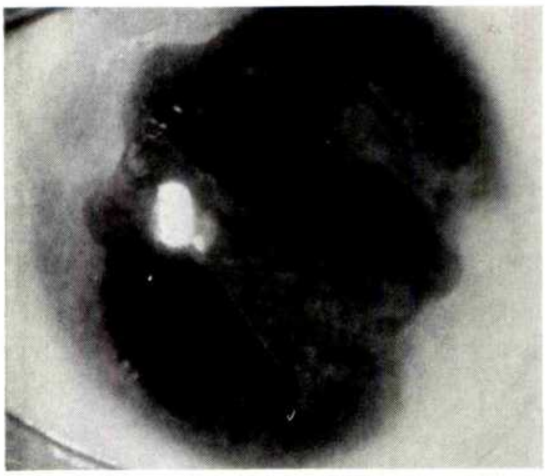

Fig. 1 *Slit-lamp photograph of left eye of proband. Note the ill-defined limbus, dyscoria, ectropion uveae, and multiple defects in the abnormal iris stroma*

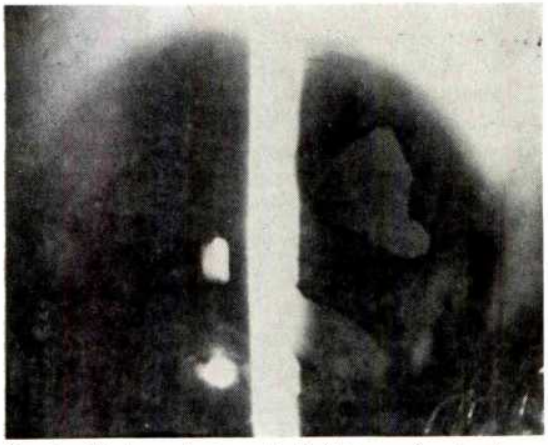

Fig. 2 *Slit-lamp photograph of right eye of proband. Note the ill-defined limbus, dyscoric pupil, and multiple defects in the hypoplastic iris stroma*

Schwalbe's line bilaterally, causing practically complete closure of the angle structures (Figs. 1 and 2). The irides were atrophic, with hypoplasia of the anterior stroma. Ophthalmoscopic examination showed normal fundi without abnormal cupping of the optic discs. Intraocular pressures were 16 mmHg in both eyes and outflow facilities C=0·25 bilaterally.

During this period the child was repeatedly examined under anaesthesia for evidence of glaucoma. There was one episode of intraocular pressure of 50 mmHg bilaterally, which was treated with pilocarpine 4% 4 times daily and acetazolamide 60 mg 4 times daily. Repeat tonometry during the following weeks gave normal pressures both off and on medication, and further drug therapy was discontinued. Dental examination showed maxillary hypoplasia and microdontia (Fig. 3).

At the age of 10 years the patient's visual acuity was 20/50 with +2·00 to 6·00×160° right eye, and 20/30 with +4·00 to 1·50×150° left eye. There was mild retraction and recession of the upper lip. Lids, orbits, and lacrimal apparatus were normal bilaterally. The range of extraocular muscle movement was full, with orthophoria at 20 ft (6 m) and 14 in (36 cm). Slit-lamp examination showed normal corneas but reduced depth of anterior chamber in both eyes. Pupils were elongated in a slit-like configuration, and large defects in the atrophic iris stroma were present.

Applanation tonometry gave intraocular pressures of 24 mmHg in the right eye, and 16 mmHg in the left. Gonioscopy of the right eye showed two small areas of open angle, superiorly and inferiorly. Schwalbe's line was abnormally thickened, and numerous iris processes were noted. The remainder of the angle was closed by peripheral anterior synechiae. The left eye had an anterior chamber angle very much like that of the right eye with many fine iris processes inserted anteriorly on to the prominent Schwalbe's line.

Goldmann perimetry showed full visual fields to 1 to 2, 1 to 3, and 1 to 4 test targets bilaterally. On ophthalmoscopic examination discs, vessels, maculae, and peripheral retinas were seen to be normal on both sides.

Karyotypes prepared from peripheral blood cultures and banded with Giemsa showed a modal

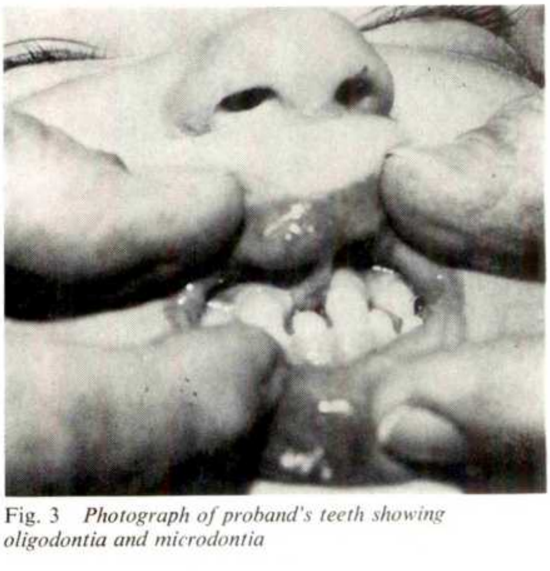

Fig. 3 *Photograph of proband's teeth showing oligodontia and microdontia*

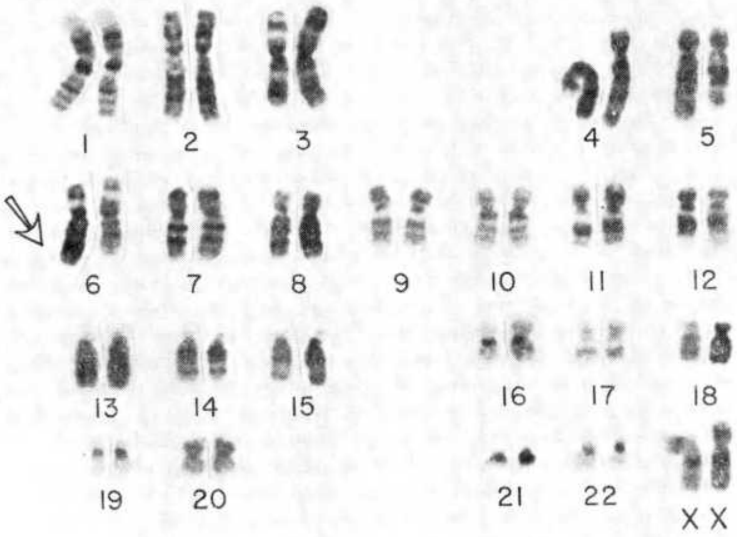

Fig. 4 *Karyotype of proband*

count of 46 with pericentric inversion of chromosome 6 (6p+q−) (Figs. 4 and 5).

CASE 2

The father of the proband is 36 years old. Visual acuity was 20/20 right eye, 20/25 left eye, without correction. External examination showed the lids, orbits, and lacrimal apparatus to be within normal limits. Slit-lamp examination revealed normal conjunctivae and corneas. Gonioscopy was remarkable for prominent Schwalbe's line and iris mounds bilaterally. On ophthalmoscopic examination discs, vessels, maculae, and peripheral retinas were seen to be normal on both sides. Intraocular pressures were 17 mmHg right eye and 15 mmHg left eye.

Karyotypes prepared from peripheral blood cultures of the proband's father showed a pericentric inversion of chromosome 6 (6p+q−).

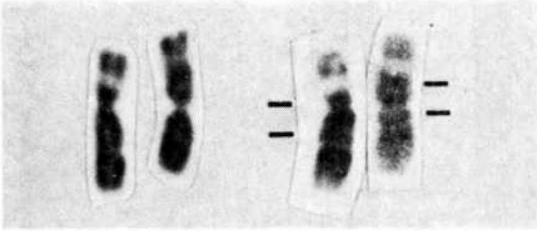

Fig. 5 *To right (between lines) chromosome 6 pair from proband showing pericentric inversion.*
To left, chromosome 6 pair of father with pericentric inversion

CASE 3

The proband's mother is 33 years old. Visual acuity was 20/20 bilaterally without correction. External appearances of the lids, orbits, and lacrimal apparatus were within normal limits. Slit-lamp examination revealed normal conjunctivae, corneas, anterior chambers, irides, and lenses. Gonioscopy revealed normal angle structures bilaterally. On ophthalmoscopic examination optic discs, vessels, maculae, and peripheral retinas were seen to be normal on both sides. Intraocular pressures were 14 mmHg right eye and 14 mmHg left eye.

Karyotypes prepared from peripheral blood cultures of the proband's mother were normal (46 XX).

Discussion

Pericentric inversions of autosomal chromosomes are rare events. Reviews of chromosomal analyses of large series of consecutive births have shown an incidence ranging from 0·16 to 0·56 per 1000 live births (Friedrich and Nielson, 1973). Ocular anomalies associated with pericentric inversions have been summarised by Jay (1977). Simple and typical colobomata of the iris have been found in 4 cases of pericentric inversions (Lele *et al.*, 1965; Schmid, 1967; Mikelsaar *et al.*, 1970). Pitt (1967) presented a case of an inversion of a C-group chromosome with associated exotropia, epicanthal folds, and hypertelorism; however, no anomalies of the iris or anterior chamber angle were noted.

The highly variable constellation of ocular and systemic defects which have been found in cases of Rieger's syndrome underscores the variance of phenotypic expression of this disorder (Alkemade, 1969). Microcornea, found bilaterally in the proband, is a relatively uncommon finding in Rieger's syndrome. Only 9% of eyes in Alkemade's series (1969) were found to have corneal diameters under 9·5 mm. Actual corneal dimensions are often hard to determine accurately, as most cases of the disorder have indistinct limbi owing to persistent corneoscleral membranes. The proband had multiple iris abnormalities including stromal defects, hypoplasia of the anterior stroma, and ectropion uveae. The dyscoric, slit-like pupils are seen in most cases of Rieger's syndrome, though the large iridal defects, pseudopolycoria, such as those found in the proband are less common (Alkemade, 1969).

Most pedigrees of families with primary mesodermal dysgenesis show considerable interfamilial variability of phenotypic expression. The minimal ocular anomalies found in the proband's father, prominent iris mounds bilaterally, may represent a mild clinical manifestation of the disease. Burian (1957) reported a similar pedigree in which the father was found to have anterior chamber angle structures and irides which were interpreted as being abnormal only after stigmata of primary mesodermal dysgenesis were discovered in 4 of his 8 children.

Defects of the anterior chamber angle and iris such as colobomata and stromal hypoplasia are found in many of the autosomal syndromes. Hypoplasia of the iris is often seen in trisomy 21 in addition to the characteristic Brushfield spots (Lowe, 1949; Caginaut, 1968). Trisomy 13-15 is notable for the extent of ocular involvement (Patau *et al.*, 1960). These patients had the signs of generalised mesodermal dysplasia. Facial cleft defects and poor differentiation of the anterior chamber angle structures are common (Apple *et al.*, 1970). The irides and choroid are usually very abnormal, often containing intraocular cartilage thought to be formed from mesodermal remnants within the ciliary body (Smith *et al.*, 1963).

The ocular anomalies associated with trisomy 18 syndrome are largely external, but intraocular defects have been found (Edwards *et al.*, 1960). Keith (1968) reviewed 5 cases and found microcornea, shallow anterior chambers, and abnormal ciliary processes in 1 case. Ginsberg *et al.* (1968) reported a case with eccentric pupils and another with iris sphincter atrophy, anomalous ciliary processes, and abnormal iris stroma.

Clinical syndromes involving chromosomal deletions also affect the iris and anterior chamber angle. Iris colobomata, sclerocornea, anterior chamber angle malformations, and ectopic pupils have been found in cases of 4p- (Wolf-Hirschorn) syndrome (François *et al.*, 1972). Glaucoma is a prominent feature of 18q- (De Grouchy) syndrome and has been reported in association with anomalies of the anterior chamber angle (De Grouchy, 1965). Ring defects of chromosome 18 (18r syndrome) are found in patients with malformations of the anterior chamber angle and iris hypoplasia (Yanoff and Rorke, 1970).

One of us (Cotlier *et al.*, 1977) presented a pedigree of partial trisomy 2q syndrome of which 2 members had prominent, anteriorly displaced Schwalbe's line and iridocorneal adhesions. Although these patients lacked the iridal stromal hypoplasia and pupillary anomalies found in Rieger's syndrome, the abnormalities of the anterior chamber angle and the presence of glaucoma suggest a similar pathogenic mechanism.

The pathogenesis of Rieger's syndrome and similar ocular malformations has yet to be established. There are few animal models for the disease, though pedigrees of basenji dogs have been studied and found to have microcornea, persistent pupillary membranes, typical colobomata involving the iris, choroid, and retina, and sclerocorneal membranes (Barnett and Knight, 1969). One dog was also noted to have missing upper premolar teeth unilaterally. The mode of inheritance was autosomal dominant. Chromosomal analyses have not been reported.

The well-documented hereditary patterns of inheritance of Rieger's syndrome and the association of chromosomal defects with aberrant development of the anterior chamber angle and iris suggest a genetically-induced defect during early morphogenesis involving the iridogenic mesoderm, probably during the 14 to 20 mm state of development. The abnormalities of the iris, pupil, and anterior chamber angle are the result of imperfect progression of the cleavage process which forms the anterior chamber. No specific chromosome can be implicated, but the genetic imbalance resulting from a chromosomal defect may be enough to upset the delicate morphogenetic process.

This case represents only the second time that a chromosomal anomaly has been associated with Rieger's syndrome. The case of Tabbara *et al.* (1973) showed ocular and systemic defects in association with an extra metacentric chromosome, similar to a G-chromosome, and a missing group C-chromosome. Clinical findings included many defects also noted in the proposita such as bilateral defects of the anterior chamber angle structures, microcornea, dyscoria, pseudopolycoria, hypoplasia of the maxilla, and anodontia. Defects of chromosome 6 have been associated with 5 cases in which defects of the

Table 1 *Aberrations of chromosome 6 with iris and anterior chamber defects*

Author	*Ocular anomalies*	*Chromosomal defect*
Rhode and Catz, 1964	Ectopic pupils	6q partial trisomy
Goddé-Jolly *et al.*, 1970	Opaque membrane over anterior chamber angle structures Glaucoma	46XX -1-C t(1p −; Cp − q+)
Tabbara *et al.*, 1973	Mesodermal dysgenesis Microcornea Glaucoma	Presumptive isochromosome of long arm of chromosome 6
Lamarr *et al.*, 1974	Obstruction of anterior chamber angle by membrane Processes extending from membrane to iris	t(1;6) q23; q27)
Tinning *et al.*, 1975	Glaucoma	t(1; 6)

anterior ocular segment and glaucoma were found (Table 1).

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Piloplex, a new long-acting pilocarpine polymer salt. A: Long-term study

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SUMMARY Thirty eyes of 15 patients with open-angle glaucoma were followed up for a period of up to 1 year while being treated with Piloplex eye drops containing a new long-acting pilocarpine polymer salt. Average morning intraocular pressure (IOP) values during treatment with pilocarpine hydrochloride administered 4 times daily was 20·5 mmHg. Average morning IOP values during Piloplex medication administered only twice daily were 19·8 to 18·2 mmHg (range of averages on 14 sessions). These findings indicate the lower average pressure during Piloplex medication and show its prolonged hypotensive effect. Both medications contained an equivalent total daily amount of pilocarpine. Throughout the 1-year study period no adverse side effects were reported, and only 1 patient complained of local sensitivity reaction. Visual disturbances characteristic of pilocarpine eye drops were reduced from 3 times a day on pilocarpine hydrochloride 4 times daily to once a day on Piloplex twice daily.

One of the major problems in the treatment of glaucoma is the limited therapeutic effect (6 to 8 hours) of pilocarpine eye drops. Consequently many attempts have been made to prolong the hypotensive effect of pilocarpine. Increase in concentration of pilocarpine above 4% has failed to show a significant increase or prolongation of therapeutic effect (Harris and Galin, 1970; Drance and Nash, 1971). Also, increased viscosity of the ophthalmic solution administered only twice daily did not give adequate control for clinical usefulness (Quigley and Pollack, 1977).

A prolongation of therapeutic effect, however, can be achieved by sustained release of pilocarpine to the ocular tissues. This is possible only when release of the drug from its vehicle is rate-limiting (Sieg and Robinson, 1977).

Piloplex emulsion, which contains a new pilocarpine polymer salt, has been designed to give sustained release of pilocarpine. This characteristic of Piloplex has been demonstrated *in vitro* by comparing the release patterns of pilocarpine hydrochloride with Piloplex. The results, summarised in Fig. 1, indicated that the release time of 80% of the active ingredient from Piloplex is 6 hours, against 1 hour for the corresponding pilocarpine hydrochloride solutions.

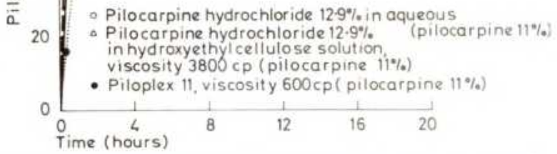

Fig. 1 In vitro *release of pilocarpine from Piloplex and pilocarpine hydrochloride solutions from a dialysis bag. The medium was an agitated isotonic saline solution (pH 7·1) maintained at 37°C. Active ingredient was determined spectrophotometrically (Ticho* et al., *1978)*

Preliminary clinical trials on 68 patients with glaucoma treated with Piloplex confirmed its

Address for reprints: Dr U. Ticho, Department of Ophthalmology, Hadassah Hospital, Jerusalem, Israel prolonged hypotensive effect (Ticho *et al.*, 1978; Blumenthal *et al.*, 1979). In these studies Piloplex administered twice daily induced a lower average diurnal intraocular pressure (IOP) level with fewer IOP fluctuations than pilocarpine hydrochloride administered 4 times daily (Fig. 2). The total daily amount of pilocarpine applied in the two different medications was equal. The present paper reports on the therapeutic effect and safety of long-term Piloplex medication.

Patients and methods

The study was carried out at 3 different glaucoma units. At the Hadassah, Sheba, and Rambam hospitals in Israel 30 eyes of 15 patients who agreed to participate in this survey with their informed consent were studied. All patients had bilateral open-angle glaucoma with visual field defects. All had been under our medical supervision for at least 2 years before this study. Ten of our patients were males and 5 were females. They were aged 48 to 84 except for 1 patient who was 18 years old. The study was divided into two periods: (1) Two-week period in which the patients were treated with their prestudy medications. These medications consisted of pilocarpine hydrochloride (PHCl) 2% or 4% 4 times daily, which contains 1·7 and 3·4% pilocarpine base. To 5 patients additional epinephrine borate (1% of free base) and/or acetazolamide 250 mg were administered twice a day. The detailed prestudy medication is listed in Table 1. (2) After the first 2 weeks of treatment PHCl 2 or 4% was replaced by Piloplex 3·4 and 6·8 twice daily respectively. Piloplex 3·4 and 6·8 contains 3·4 and 6·8% pilocarpine.

Table 1 *Patients and medication data*

Patients			*Prestudy medicine*	*Study medicine*	*Study duration*
No.	*Age*	*Sex*	*(period A)*	*(period B)*	*(months)*
1	65	F	PHCl 2	PX 3·4	12
2	66	M	PHCl 2	PX 3·4	8
3	78	M	PHCl 2	PX 3·4	12
4	76	M	PHCl 2	PX 3·4	8
5	65	M	PHCl 2	PX 3·4	11
6	73	M	PHCl 2, E	PX 3·4, E	9
7	18	F	PHCl 2, E, AC	PX 3·4, E, AC	8
8	54	M	PHCl 4	PX 6·8	12
9	61	M	PHCl 4	PX 6·8	12
10	65	F	PHCl 4	PX 6·8	12
11	49	F	PHCl 4	PX 6·8	12
12	69	M	PHCl 4, AC	PX 6·8, AC	12
13	52	M	PHCl 4, E, AC	PX 6·8, E, AC	8
14	84	F	PHCl 4, E, AC	PX 6·8, E, AC	9
15	60	M	PHCl 4, E, AC	PX 6 8, E, AC	12

Abbreviations for medications administered are as follows: PHCl — pilocarpine hydrochloride given 4 times daily (number following PHCl indicates the percentage of PHCl). PX — Piloplex given twice daily (number following PX indicates the percentage of pilocarpine). E — epinephrine borate (1% of free base) given twice daily. AC — acetazolamide 250 mg given twice daily.

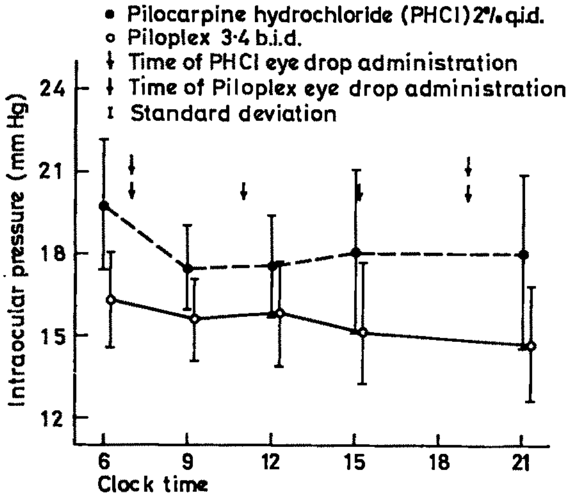

Fig. 2 *Average diurnal IOP curve of 21 eyes (12 hospitalised patients) on the third day of pilocarpine hydrochloride 2% 4 times daily treatment and on the third day of Piloplex 3·4 twice daily treatment (Blumenthal* et al., *1979)*

Morning intraocular pressures were measured by the Goldmann applanation tonometer before medications on day 14 of period *A* and on days 7, 14, and 28 and every month thereafter through 8 to 12 months of period *B*. At each visit tolerance and side effects were recorded. Visual fields were obtained every 3 months.

Results

Out of the 30 eyes studied 26 (87%) had an IOP of less than 24 mmHg throughout all measurements over an 8- to 12-month period. None of the patients presented progression in field loss. Average morning IOP of the 30 eyes at the end of the first 2 weeks of PHCl 4 times daily (period *A*) was 20·5 mmHg. This value was higher than those measured during the 8 to 12 months of Piloplex twice daily (period *B*) (range of average morning IOP values: 19·8 to 18·2 mmHg). The average morning IOP curve throughout

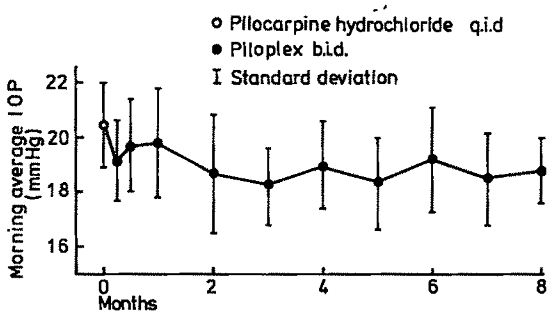

Fig. 3 *Average morning IOP curve of the 30 eyes studied during pilocarpine hydrochloride 4 times daily medication (period* A*) followed by Piloplex twice daily treatment (period* B*)*

the study period is illustrated in Fig. 3. In the 5 patients to whom epinephrine drops were administered in addition to Piloplex an anticipated additive effect was observed, similar to that found with the use of PHCl and epinephrine.

No signs of ocular damage followed Piloplex medication. Specifically, no corneal abrasions, conjunctival reactions, or inflammations were observed. One case was excluded owing to a local sensitivity reaction (No. 13), and 1 (No. 4) died of an unrelated cause. Those patients who had undesirable myopia, induced by miotic drugs following Piloplex administration (10/15), reported that Piloplex caused a similar effect to that caused by PHCl during period *A*. All patients reported that on the Piloplex regimen blurring occurred only once a day (morning dose) instead of 3 times a day while on pilocarpine hydrochloride 4 times daily.

Discussion

In our previous study we demonstrated the slow release of pilocarpine ion from the pilocarpine polymer salt compound Piloplex (Ticho *et al.*, 1978). In further clinical studies (Ticho *et al.*, 1978; Blumenthal *et al.*, 1979) Piloplex emulsion was found to be more effective in maintaining round-the-clock IOP than PHCl. Moreover, Piloplex was better than PHCl in maintaining a significantly lower mean IOP with less variation in diurnal values. Furthermore, these results were achieved by 2 applications per day of Piloplex instead of 4 applications of PHCl.

In this long-term study Piloplex was shown to be a safe drug which maintains its hypotensive effects. Systemic side effects were not present, and local sensitivity was found only in 1 patient out of the 15 studied. Over the long-term period the patients became accustomed to this medication, and subjectively preferred it to PHCl, mainly because of the twice daily regimen. Adverse visual disturbances were also reported to occur less owing to the fewer daily applications of Piloplex. In conclusion, this study has shown the long-term therapeutic effect and safety of Piloplex medication throughout a trial period of 1 year.

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Piloplex, a new long-acting pilocarpine polymer salt. B: Comparative study of the visual effects of pilocarpine and Piloplex eye drops

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SUMMARY Induced accommodation and changes in vision (distance and near) were measured monocularly and binocularly in 9 young healthy volunteers in a double blind study after administering to them pilocarpine hydrochloride 4%, Piloplex 3·4, and saline eye drop instillations. Piloplex 3·4, a new long-acting pilocarpine polymer salt, and pilocarpine hydrochloride 4% (both contain equal amounts of pilocarpine—3·4%) induced changes in vision and accommodation. These changes were greater with pilocarpine hydrochloride than with Piloplex. The maximum changes occurred half an hour after instillation and the effect vanished after an additional period up to 3 hours. The changes were greater when measured monocularly than binocularly. Piloplex initiates a prolonged hypotensive effect which lasts for 12 hours. Patients with glaucoma are thus able to use Piloplex on a twice-daily schedule. Consequently, visual disturbances occur only once a day in contrast to pilocarpine hydrochloride given 4 times a day, which induces 3 visual disturbances during the day.

The advantage of Piloplex—a new pilocarpine polymer salt—over pilocarpine hydrochloride (PHCl) has been previously presented (Ticho *et al.*, 1978; Blumenthal *et al.*, 1979). Piloplex eye drops were found to have a prolonged and increased hypotensive effect, allowing them to be given on a twice-daily schedule in contrast to a 4-times daily schedule necessary for PHCl. The hypotensive effect of miotic drugs, however, is accompanied by miosis and accommodative spasm, inducing blurred vision. These side effects are predominant in young patients (Place *et al.*, 1975; Brown *et al.*, 1976). Adverse side effects of this nature have not been encountered with Piloplex treatment so far.

This communication reports on a study in which the induced visual effects of pilocarpine hydrochloride and Piloplex were compared in young normal persons.

Patients and methods

Nine medical students who had no record of ophthalmic disturbances were selected for the study. On ophthalmic examination before the study all the students had 20/20 visual acuity in both eyes, 4 of them having spectacle corrections. Their informed consent was obtained after a detailed explanation of the study.

The group consisted of 7 men and 2 women, ranging in age from 24 to 31 years. Three of them had green eyes, 3 had brown eyes, 2 had grey-blue eyes, and 1 had hazel eyes. They were examined during 3 daily sessions and were assigned randomly to 3 different eye drop treatments: (1) Pilocarpine hydrochloride 4%; (2) Piloplex 3·4 (Hydrophilics); and (3) isotonic saline. The first 2 eye drop preparations contained equivalent amounts of pilocarpine ion. In each session 1 eye drop was instilled into each eye (both eyes were treated similarly). Successive sessions with different medications were performed 3 or 4 days apart.

All examination sessions included subjects receiving all 3 types of treatments. Subjects were examined in random order. Neither the tested subject nor the examiner knew which of the medications were tested at each examination.

The examinations were of visual acuity and induced accommodation. The visual acuity was determined at 20 ft (6 m) by a Snellen projector

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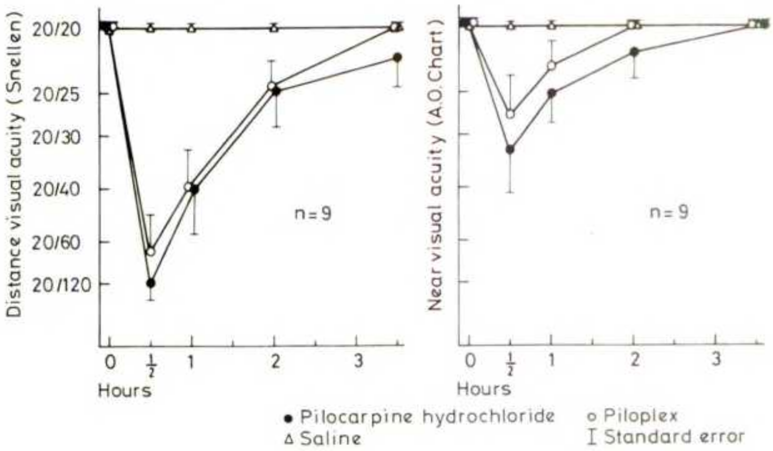

Fig. 1 *Average changes in visual acuity of 9 normal persons after pilocarpine hydrochloride 4%, Piloplex 3·4, and saline eye drops*

chart of numbers. Near vision was evaluated at 13 in (33 cm) with the American Optical Company near-point chart (AO). The induced accommodation was estimated by measuring the 'plus to blur' error. Where there was a reduction of visual acuity, normal vision was restored by adding minus lenses. The amount of minus power was then reduced until the person again reported blurred vision. The difference in the power of the lenses to induce blurring before and after medication was considered to be the amount of induced accommodation. Measurements of visual acuity and induced accommodation were performed for distance and near vision with each eye separately and with both eyes together.

All examinations were performed immediately before medication (zero time) and at 30, 60, 120, and 210 minutes after the administration of eye drops. Results were statistically examined by the Wilcoxon matched pairs signed rank test.

Results

DISTANCE AND NEAR VISION

Vision was reduced in the 9 students at distance and near vision after instillation of both types of pilocarpine eye drops (Fig. 1). The maximum reduction was half an hour after instillation. Distance vision returned to normal after a further 3 hours, while near vision returned to normal 2 hours after instillation of Piloplex and 3½ hours after instillation of PHCl.

PHCl induced a larger visual effect than Piloplex, but the difference was not significant. The visual effect caused by both pilocarpine medications was stronger when measured on a single eye than on both eyes. Distance vision was reduced to less than 20/100 30 minutes after instillation of PHCl in 6 out of the 9 persons when measured with both eyes open. However, when the vision of each eye was measured separately it was reduced to 20/100 in 16 out of 18 eyes 30 minutes after instillation. Near vision was reduced to less than 20/50 30 minutes after instillation of PHCl in 3 out of the 9 persons, while 9 out of the 18 eyes showed similar reduction of vision at the same time.

INDUCED ACCOMMODATION MEASURED AT DISTANCE AND NEAR

Induced accommodation was measured in all 9 students at distance and near vision after instillation of both types of pilocarpine eye drops. The maximum change in induced accommodation was reached 30 minutes after instillation and gradually wore off during the next 3 hours (Fig. 2). PHCl caused a larger change in accommodation than Piloplex, but the difference was not significant. Change in accommodation was greater when measured monocularly than with both eyes open at distance (Fig. 3) and at near vision with both medications.

Changes in vision and induced accommodation were fairly consistent throughout the study with both medications. Persons who showed the greatest change on induced accommodation also showed the greatest changes in distance and near vision.

Discussion

Pilocarpine causes hypotensive and visual effects which can be measured by changes in intraocular pressure, vision (distance and near), refraction, and miosis. Changes in vision and refraction, however, are not directly dose-related to the concentration of pilocarpine in the eye. Thus, constant delivery of

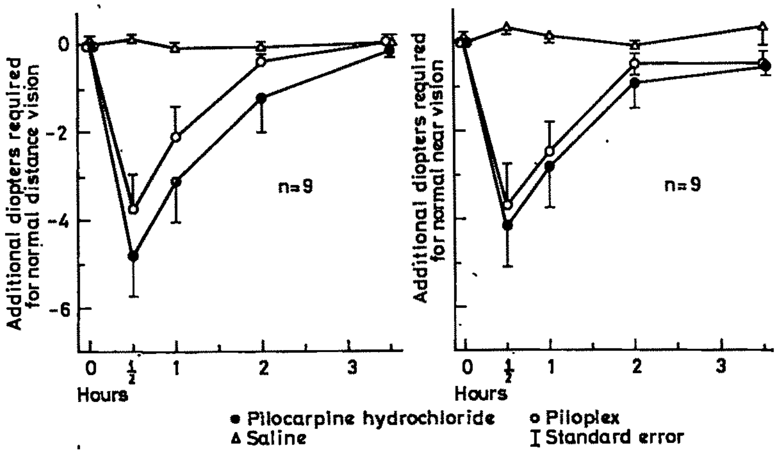

Fig. 2 *Average amount of induced accommodation, expressed as 'plus to blur' measurement for distance vision (left) and near vision (right) of 9 normal persons after pilocarpine hydrochloride 4%, Piloplex 3·4, and saline eye drops*

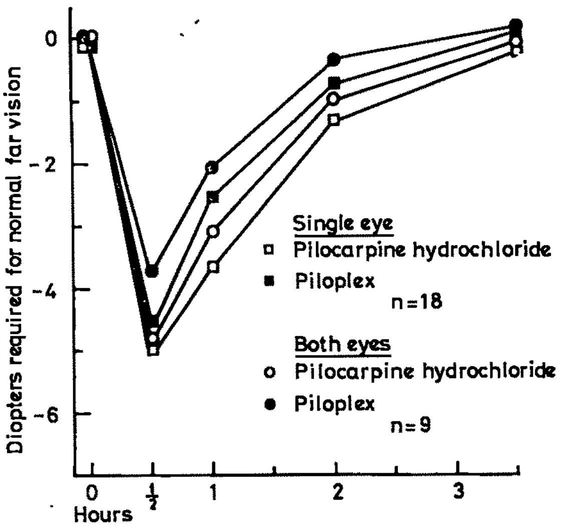

Fig. 3 *Average induced accommodation measured monocularly and with binocular vision of 9 normal persons after pilocarpine hydrochloride 4% and Piloplex 3·4 eye drops*

small amounts of pilocarpine (20 μg/h by Ocusert) produced visual, effects—refraction, distance and near vision—which did not substantially differ from those initiated by delivery of 40 μg/h of pilocarpine. Miosis and hypotensive effects were stronger after higher doses (Brown *et al.*, 1976). Thus miosis and ocular hypotension appear to be more sensitive to relatively low doses of pilocarpine than refractive changes and distance and near vision.

Changes in all parameters are reported when the amount of pilocarpine is increased, ranging from 1 to 4%, and the changes were dose-related (Brown *et al.*, 1976). It is expected that saturation of the pilocarpine binding sites will create the maximum visual effect, and higher doses will cause no further changes. Quigley and Pollack (1977) reported experiments with 2 different viscous preparations of PHCl (same pilocarpine dose). Green and Downs (1975) when using these preparations found different pilocarpine levels in rabbit aqueous humour. However, no significant intraocular pressure difference was reported comparing the hypotensive effect of these 2 different preparations in patients (Quigley and Pollack, 1977).

The present study shows that very similar changes in refraction and far and near vision were induced by Piloplex and PHCl, thus hinting that during the first period after instillation of the drug the amount of pilocarpine in the eye is much the same from each of the two pilocarpine preparations. However, the fact that Piloplex causes a longer hypotensive effect than PHCl (Ticho *et al.*, 1978; Blumenthal *et al.*, 1979) suggests that later on after instillation the amount of pilocarpine in the eye from PHCl is no longer sufficient to maintain a hypotensive effect. In contrast, in the later period after instillation of Piloplex there is sufficient pilocarpine in the eye to provide a longer-lasting hypotenstive effect but without inducing visual disturbances. A similar situation was reported for Ocusert (Brown *et al.*, 1976).

Piloplex, a salt, releases pilocarpine ion at a sustained rate (Ticho *et al.*, 1978) and initiates a prolonged hypotensive effect lasting 12 hours; it therefore can be given on a twice daily schedule. Since adverse visual effects after evening medication (instilled before night sleep) do not disturb the patient, it could be concluded that Piloplex induces visual disturbances only once a day (after the morning medication) in contrast to PHCl on a 4 times daily schedule, which induces 3 disturbances during the daytime.

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Evaluation of a 5% guanethidine and 0·5% adrenaline mixture (Ganda 5·05) and of a 3% guanethidine and 0·5% adrenaline mixture (Ganda 3·05) in the treatment of open-angle glaucoma

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SUMMARY A trial of a mixture of guanethidine 5% and adrenaline 0·5% (Ganda 5·05) and of guanethidine 3% and adrenaline 0·5% (Ganda 3·05) was conducted on 90 eyes in 53 patients with open-angle glaucoma or ocular hypertension. The cases fell into 5 groups: untreated cases, cases on pilocarpine 1%, on pilocarpine 2%, on pilocarpine 2 to 4% and adrenaline 1%, and on separate guanethidine 5% and adrenaline 1%. Baseline pressures and average pressures on the previous treatment were established. Substitution with Ganda 3·05 or 5·05 was started, and the patients attended 2 weeks, 1 month, 3 months, and 6 months from the start of the trial. Applanation tonometry was carried out at the same time of day. The pupil was measured, ptosis and superficial punctate corneal staining were looked for and evaluated, and the patients were questioned for symptoms of side effects and acceptability. All the eyes that had previously been treated with pilocarpine 1% or 2% presented significantly lower intraocular pressures on Ganda 3·05. The patients on pilocarpine 4% and adrenaline 1% also had lower intraocular pressures on Ganda 5·05, but the significance was less, and the patients on separate guanethidine and adrenaline had a small but not statistically significant drop in pressure. Ptosis and discomfort were evaluated on a subjective scale. Patient acceptability was good. The trial was interrupted in 5 cases for various reasons. Tachyphylaxis and tolerance to the mixtures were not observed in this series.

Interest in guanethidine and other beta-blocking agents for the possible lowering of intraocular pressure goes back to the early 1960s. Guanethidine eye drops were being successfully used to diminish the lid retraction produced by sympathetic overactivity associated with thyrotoxicosis. However, attempts by one of us (J.R.) to control the intraocular pressure in several cases with both thyrotoxicosis and open-angle glaucoma with topical guanethidine were not successful. Other workers (Stepanik, 1961; Castren and Pohjola, 1962; Anselmi *et al.*, 1968) reported a lowering of the intraocular pressure using guanethidine alone. The discrepancy between these results will be discussed later in this paper. The combination of adrenaline with guanethidine provided a breakthrough (Paterson and Paterson, 1972), and several studies attest to the efficacy of this combined therapy (Roth 1973; Gloster, 1974; Crombie, 1974; Paterson *et al.*, 1975; Etienne, 1975; Nagasubramanian *et al.*, 1976). These trials were practically all concerned with new and untreated cases of glaucoma or cases in which all previous treatment had been discontinued. More recently a trial was carried out on severe cases of open-angle glaucoma most of which were already on maximal medical therapy. The addition of guanethidine and adrenaline eye drops to the previous treatment led to a satisfactory response in most cases (Romano, 1977). The guanethidine and adrenaline eye drops were used 10 minutes apart to enhance absorption (Phillips, 1971), and this was repeated twice a day. It was felt that a mixture of the 2 drugs would be more convenient for the patient. However, it was not known at the time whether it would be possible to mix the 2 drugs in a stable solution and whether the efficacy and absorption of the mixture would be adequate. The availability of such a mixture has made this study possible.

Material and methods

The study covers 90 eyes in 53 patients drawn from the Glaucoma Clinics of both branches of Moor-

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fields Eye Hospital, London, and that of Hillingdon Hospital. Its object is to study the effect of a guanethidine 5% and adrenaline 0·5% mixture (Ganda 5·05*) and of a guanethidine 3% and adrenaline 0·5% mixture (Ganda 3·05*) on patients with open-angle glaucoma and ocular hypertension. The patients fall into the following categories: (1) Untreated cases (15); (2) cases previously on pilocarpine 1% 2 to 4 times a day or pilocarpine 2% 3 to 4 times a day (19 cases); (3) patients on pilocarpine 2 or 4% 4 times a day with adrenaline 1% twice a day (16 cases); (4) patients previously on separate guanethidine 5% and adrenaline 1% twice a day (36 cases). The main object of the trial was to study, in the treated groups, the effect of substitution of Ganda 3·05 and Ganda 5·05 for the previous treatment.

The baseline intraocular pressure was noted, and the average intraocular pressure on the previous treatment was established by recording all previous tensions and averaging the results. All pressures were estimated with the Goldmann applanation tonometer at approximately the same time each day to offset the possible effect of diurnal variations. The patients were started on the mixture, and attended 2 weeks, 1 month, 3 months, and 6 months from the onset of the trial. A pressure of 20 to 22 mmHg or lower was accepted as evidence of control. If this was not achieved after 2 weeks the treatment was continued for another 2 weeks, as it has been suggested (Paterson and Paterson, 1972) that the guanethidine-adrenaline combination may not reach its full effect until after a month or so of treatment. If still uncontrolled after a month a case would be considered to be a failure and additional or alternative treatment prescribed. At each visit the pupils were measured, either on the Goldmann perimeter with a background illumination setting of 31·50 apostilb, or on the Haag-Streit slit lamp with a graticule eyepiece and the slit beam narrowed to the 1.0 setting and directed at an angle of 30° from the temporal side.

At each visit the following were searched for and estimated: Ptosis (measured in millimetres); hyperaemia of the bulbar conjunctiva and of the eyelids, and lid-sensitivity reaction; punctate epitheliopathy, by fluorescein staining of the cornea.

The patients were closely questioned for symptoms such as discomfort, browache, burning, and blurring of vision. The fields of vision, charted before the trial, were compared with those at the end of the trial.

At the end of the trial, the average intraocular pressures, average pupil diameter, and degree of ptosis were noted. The symptoms were assessed on a subjective scale: Discomfort was described as nil, minimal (m), moderate (M), or severe (S). Ptosis was described as nil, minimal (1 to 2 mm), moderate (2 to 3 mm), or severe (more than 3 mm). Punctate epitheliopathy was described as present (+) or absent (−).

Results

See Tables 1 and 2 for analysis of results.

In 9 out of 9 cases previously on pilocarpine 1% 2 to 4 times a day compared with Ganda 3·05 the average pressure was lower on the guanethidine-adrenaline mixture. The average intraocular pressure on pilocarpine 1% was 24 mm (SD 2·1), and on Ganda 3·05 18·20 mm (SD 2·7) ($t = 10{\cdot}9$, $P \leq 0{\cdot}001$).

All 10 cases previously on pilocarpine 2% 3 to 4 times a day compared with Ganda 3·05 had

Table 1 *Analysis of all cases on Ganda 3·05*

Average fall of intraocular pressure			
At 2 weeks	*At 1 month*	*At 3 months*	*At 6 months*
10·14 mm (SD, 0·72)	10·88 mm (SD, 0·62)	10·57 mm (SD, 0·64)	9·84 mm (SD, 0·66)
Percentage fall of intraocular pressure			
37% (SD, 2·1)	39% (SD, 1·6)	38% (SD, 1·8)	36% (SD, 1·9)

Table 2 *Study of the different groups of cases for accommodation to Ganda*

Previous treatment:	*IOP at 2 weeks (mmHg)*	*IOP at 4 weeks (mmHg)*	*IOP at 3 months (mmHg)*	*IOP at 6 months (mmHg)*
Cases previously on:				
pilocarpine 1%	18·3 (SD, 2·9)	18·3 (SD, 1·3)	17·7 (SD, 4·0)	19·2 (SD, 4·5)
pilocarpine 2%	15·5 (SD, 2·3)	15·9 (SD, 2·7)	16·1 (SD, 3·8)	16·4 (SD, 4·3)
pilocarpine 2 to 4% and adrenaline 1%	19·2 (SD, 4·0)	17·3 (SD, 4·3)	17·2 (SD, 5·7)	19·3 (SD, 4·1)
separate guanethidine 5% and adrenaline 1%	18·1 (SD, 3·2)	18·4 (SD, 3·0)	17·8 (SD, 3·1)	17·4 (SD, 3·7)
Untreated cases	20·6 (SD, 1·73)	18·4 (SD, 1·62)	19·0 (SD, 1·0)	19·9 (SD, 1·5)

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*Supplied by Smith & Nephew Pharmaceuticals, Welwyn Garden City, Herts. Ganda is short for Guanethidine AND Adrenaline.

lower average intraocular pressure on Ganda. The average intraocular pressure on pilocarpine 2% was 21·8 mm (SD 2·7), and on Ganda 3·05 16·0 mm (SD 2·9) (t=5·68, P<0·002).

In the 6 cases previously on pilocarpine 2–4% 3 to 4 times a day and adrenaline 1% twice a day compared with Ganda 5·05: 10 eyes had lower pressure on Ganda 5·05, 3 eyes had the same pressure on Ganda 5·05, and 3 eyes had a higher pressure on Ganda 5·05. The average intraocular pressure on pilocarpine 2 to 4% and adrenaline was 20·1 mm (SD 2·7), and on Ganda 5·05 18·7 mm (SD 3·1) (t=2·45, P⩽0·05).

In the cases previously on separate guanethidine 5% and adrenaline 1% compared with Ganda 5·05 16 eyes had lower pressure on Ganda 5·05, 19 eyes higher pressure on Ganda 5·05, and 1 eye the same pressure. The average intraocular pressure on separate guanethidine 5% and adrenaline 1% was 18·29 mm (SD 2·2), and on Ganda 5·05 17·92 mm (SD 2·7) (t=0·75, P⩾0·05).

All 15 untreated cases had their average intraocular pressures lowered by Ganda 3·05. The average untreated intraocular pressure was 26·36 mm, and on Ganda 3·05 it was 18·45 mm.

As to side effects in 86 eyes: discomfort was absent in 28 cases, minimal in 45, moderate in 13, and severe in none. Ptosis was absent in 12 cases, minimal in 44 (16 on Ganda 3·05, 24 on Ganda 5·05), moderate in 26 (6 on Ganda 3·05, 17 on Ganda 5·05), and severe in 4 (all on Ganda 3·05). Hyperaemia of variable degree noted in 30 cases.

Discussion

It is now fairly widely accepted that topical guanethidine induces a state of 'chemical sympathectomy' in the autonomic nervous system of the anterior segment of the eye, rendering the postganglionic receptors hypersensitive to the action of the chemical transmitter adrenaline. In a recent communication (Romano, 1977) two possibilities regarding the mode of action of guanethidine were invisaged: (1) The hypersensitisation effect is created anew, or at least 'topped up' with each instillation of guanethidine; (2) it gradually builds up over several days with repeated instillations.

If the first view is the correct one, separate administration of guanethidine followed by adrenaline after a suitable interval would be the logical way to use the drugs. However, in some cases the effect of these drugs has been observed (Paterson and Paterson, 1972) to be delayed for some weeks, which supports the second view. Furthermore, the use of a mixture of the 2 substances has proved to be at least as effective—and in the present series it has been marginally more successful—than that of separate administration. If this is so, the added convenience to the patient of a single instillation must make the mixture the treatment of choice.

In this context the difference in the success-rate reported by various workers with topical guanethidine *alone* is interesting.

SIDE EFFECTS

Ganda has been well tolerated by the patients in this trial, the intolerance rate being around 5·5%. This improved tolerance can be attributed to the use of 0·5% adrenaline instead of the more traditional 1% solution. Discomfort, when present, was usually an initial sensation of grittiness and browache, passing off with continued use of the drops. It was often transient, lasting a minute or two only. As regards ptosis, in 1 case vision was impaired by a 'severe' ptosis of 3 to 4 mm. Although minimal ptosis was a frequent finding, the patients were usually unaware of it. Moderate or severe ptosis could cause some cosmetic disability. Hyperaemia was severe in a dozen or so cases; it was certainly not so marked as has been observed with 1% adrenaline. Punctate epitheliopathy, a rare finding, was associated, when present, with discomfort in about half the cases.

Five cases were rejected from the trial for intolerance to the drops, probably to adrenaline; 1 case for poor control of pressures with small visual fields; and 2 cases for mistakenly using pilocarpine along with Ganda for one or more visits.

Where little or no hypertensive effect is achieved, it may be speculated that local or circulating catecholamines are not sufficient in some individuals, in spite of the hypersensitisation of the adrenergic receptors, to produce a significant lowering of the intraocular pressure, the reverse being true in other individuals.

VISUAL FIELDS

There was no evidence of field loss or of any increase in pre-existing field loss in any patient during the 6-month period of the trial. As mentioned above, 1 case with previously very constricted fields was withdrawn from the trial as his intraocular pressures were considered to be insufficiently controlled.

TACHYPHYLAXIS AND ACCOMMODATION TO GANDA

Tachyphylaxis, defined as the loss of effectivity of a a drug occurring early (i.e., in the first few days of treatment), was not specifically studied. It is, however, unlikely to occur, as guanethidine and adrenaline mixtures appear gradually to build up to their maximum effectivity, often over the first few weeks. *Accommodation,* defined as a gradual loss of effectivity over a longer period, did not seem to occur in this series (Tables 1 and 2).

Conclusion

In our series the ocular hypotensive action of Ganda 3·05 was significantly greater than that of pilocarpine 1% 2 to 3 times a day, pilocarpine 2% 3 to 4 times a day, and of pilocarpine 2 to 4% 4 times a day, with adrenaline 1% twice daily. Most patients were grateful to be relieved partly of the miosis produced by pilocarpine. Compared with separate instillation of guanethidine 5% and adrenaline 1% twice daily, the average intraocular pressure was lower on Ganda 5·05 twice daily, but the difference was small (one must remember, however, that 1% adrenaline was being compared with 0·5% adrenaline). The absence of a significant difference between the separate use of the drugs and that of a mixture argues in favour of using the mixture. Our elderly glaucoma patients certainly found it easier to manage. Well over half—32 out of 53 patients—were happy with the drops, and many wished to continue with Ganda when the trial was over.

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The combination of guanethidine 3% and adrenaline 0·5% in 1 eyedrop (GA) in glaucoma treatment

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SUMMARY During a 7-month period 33 patients (20 with primary open-angle glaucoma and 13 with suspected glaucoma) were treated with guanethidine 3% and adrenaline 0·5% in 1 eyedrop twice daily. The previous therapy was discontinued and the aim of the trial was to treat the patients with GA alone. There was an average decrease in intraocular pressure of 10·8 mmHg or 37·5% for the whole group (including 5 patients with additional therapy). In eyes with an average IOP in a day-curve without medication equal to or higher than 28 mmHg we found a decrease in IOP of 44·6% or 14·4 mmHg, and in eyes with an average IOP without medication between 21 and 28 mmHg a decrease of 30·4% or 7·6 mmHg. With GA alone the IOP was 3·3 to 3·9 mmHg lower than on the previous therapy ($P < 0{\cdot}05$); 46% of the eyes without additional therapy had all IOPs lower than 22 mmHg and 74% of the eyes had IOPs lower than 22 mmHg except 1 with a peak lower or equal to 25 mmHg 3 hours after application. This peak 3 hours after application indicates that GA has a biphasic action and was significant at the 0·5% level. Red eyes and slight ptosis were no problem for most patients. Patients found it very convenient to administer GA only twice daily.

During the last 10 years non-miotic therapy has taken a more important place in the treatment of glaucoma patients suspected of having glaucoma and primary open-angle glaucoma (POAG). One of the non-miotic preparations used is a combination of guanethidine and adrenaline. Stepanik (1961), Kutschera (1961), Küchle (1961), Oosterhuis (1962), and Bonomi and di Comite (1967) reported a fall in intraocular pressure (IOP) with guanethidine 10% alone in the treatment of patients with POAG. This fall was only temporary. Sears (1966) showed in studies on patients with Horner's syndrome 'that the outflow mechanism can be made supersensitive to topical epinephrine'. G. D. and G. Paterson (1972, 1974) pointed to the phenomenon of hypersensitivity of the receptor for sympathomimetic drugs during chemical denervation with guanethidine and to the necessity of applying adrenaline twice daily during the treatment with guanethidine. Long-term studies on guanethidine and adrenaline in patients with glaucoma have been done by Roth (1973), Etienne (1973), Crombie (1974), Gloster (1974), Romano (1974, 1977), Nagasubramanian *et al.* (1976), and Jones *et al.* (1977) with good results.

The aim of the trial reported here was to investigate the possibility of stopping all previous therapy of patients known to have POAG or suspected of having glaucoma, to treat them only with guanethidine 3% and adrenaline 0·5% (GA) in 1 eyedrop, and to investigate the proper dosage of GA. New patients with POAG or new glaucoma suspects were, if possible, treated only with GA. Thus we obtained an impression of the efficacy of GA alone and its effect in relation to previous therapy.

Patients and methods

Thirty-three patients (23 male and 10 female) with either POAG or suspected glaucoma were admitted to the trial. They were divided into 20 patients with POAG (33 eyes, 2 eyes having been previously operated on) and 13 glaucoma suspects (26 eyes). The mean age of the patients was 60 years (range 25 to 84 years), and treatment lasted for an average of 7 months (range 1 to 11 months).

Our criteria for diagnosing primary open-angle glaucoma were visual field defect and/or disc

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pathologically excavated and/or in a day-curve without medication 1 pressure higher than 36 mmHg, and with an open angle. Our criteria for glaucoma suspects were no visual field defect, normal disc, in the day-curve without medication at least 1 pressure higher than 25 mmHg and lower than 36 mmHg, and with an open angle. If a patient had one eye with glaucoma and the fellow eye showed only a raised IOP, both eyes were regarded as having POAG. These criteria are arbitrary. In our clinic we prefer to use the term glaucoma suspect instead of ocular hypertension.

Before the patients were admitted to the trial they were evaluated. Visual acuity and refraction were tested, biomicroscopy with the Haag-Streit slit lamp, and gonioscopy with the 3-mirror contact lens of Goldmann were undertaken, and visual fields were tested on a Tübingen perimeter. Patients were taken off treatment 1 week before the trial if they had been on sympathomimetics and carbonic anhydrase inhibitors and 48 hours beforehand if on miotics. A day-curve without medication was then made. The IOP was taken with a Goldmann applanation tonometer mounted on a Haag-Streit slit lamp at 9 a.m. and 12 noon (0 to 3 hours) and 3 p.m. and 5 p.m. (6 to 8 hours). The previous therapy which was stopped in these patients is shown in Table 1.

After a day-curve without medication all patients started with GA twice daily at an interval of 12 hours (at 9 a.m. and 9 p.m.). The day-curves were repeated after treatment for 1 week, 1 month, 3 months, and 7 months, and then medication with GA was stopped for 2 weeks, when the day-curve was repeated. GA was given after the first pressure reading in the day-curve. Thus the first reading (at zero) gave the IOP 12 hours after the last application. Additional therapy was given to patients in whom the IOP was not sufficiently lowered. Every month during the trial the patients were examined at our polyclinic for a short control period when we checked visual acuity, refraction, and IOP, and looked for side effects. Visual fields were controlled during our trial, and we particularly looked for changes in the early defects.

In the group with 20 patients with POAG 2 left the trial (1 patient died suddenly, and 1 left for personal reasons). Additional therapy in this group was needed in 4 patients. One patient needed acetazolamide once daily plus pilocarpine 2% 4 times daily. One (who died suddenly) needed acetazolamide once daily. One needed acetazolamide once daily and carbachol 1·5% 3 times daily. And 1 patient received only pilocarpine 2% twice daily. The rest of the group was controlled with GA twice daily only.

Table 1 *Previous therapy of 20 patients with POAG and 13 with suspected glaucoma*

20 patients with POAG (n=33)	*No. of eyes*	*13 glaucoma suspects (n=26)*	*No. of eyes*
Pilocarpine 2% 4×d	14	Pilocarpine 1% 4×d	4
Aceclidine 2% 4×d	3	Pilocarpine 2% 4×d	10
Aceclidine 2% 2×d	2	Isoptocarpine 4×d	4
Aceclidine 2% + adrenaline 1% 2×d	5	Aceclidine 5×d	2
Eserine 0·25% 4×d	3	Eserine 0·25% 4×d	2
Carbachol 1·5% 3×d	2	Adrenaline borate 1 or 2×d	10
Adrenaline borate 1% 2×d	15	L-adrenaline bitartrate 2×d	2
Ismelin 5%	3	Ismelin 5% 2×d	2
Acetazolamide sustained release 1×d	4	2 or 3×0·5 Acetazolamide	6
Acetazolamide 0·250 2 or 3×d 0·5	4	None	4
None	5		

×d = times a day. Aceclidine = 3-acetoxyquinuclidine HCl

In the group with suspected glaucoma 1 patient was taken off medication with GA because of transient serous maculopathy. She was known to have had maculopathy previously. One patient needed additional therapy with pilocarpine 1% twice daily. The rest of the group was controlled with GA twice a day only.

Our results were statistically evaluated by Student's *t* test.

Results

Fig. 1 and Table 2 show the combined results of all patients treated with GA for about 7 months. The average decrease in IOP for all patients (patients with additional therapy included) was 10·8 mmHg or 37·5%, with a reduction in fall of IOP to 7·4 mmHg or 26·7% after 3 hours. After 7 months' treatment the fall in IOP was still continuing and no adaptation was seen.

We have selected the eyes of patients who had no additional therapy in 2 groups. The first group with 22 eyes had an average IOP in a day-curve without medication higher than or equal to 28 mmHg. In the second group 25 eyes had an average IOP in a day-curve without medication between or equal to 21 and 28 mmHg (28 mmHg is about the median IOP of the averaged IOPs of the individual day-

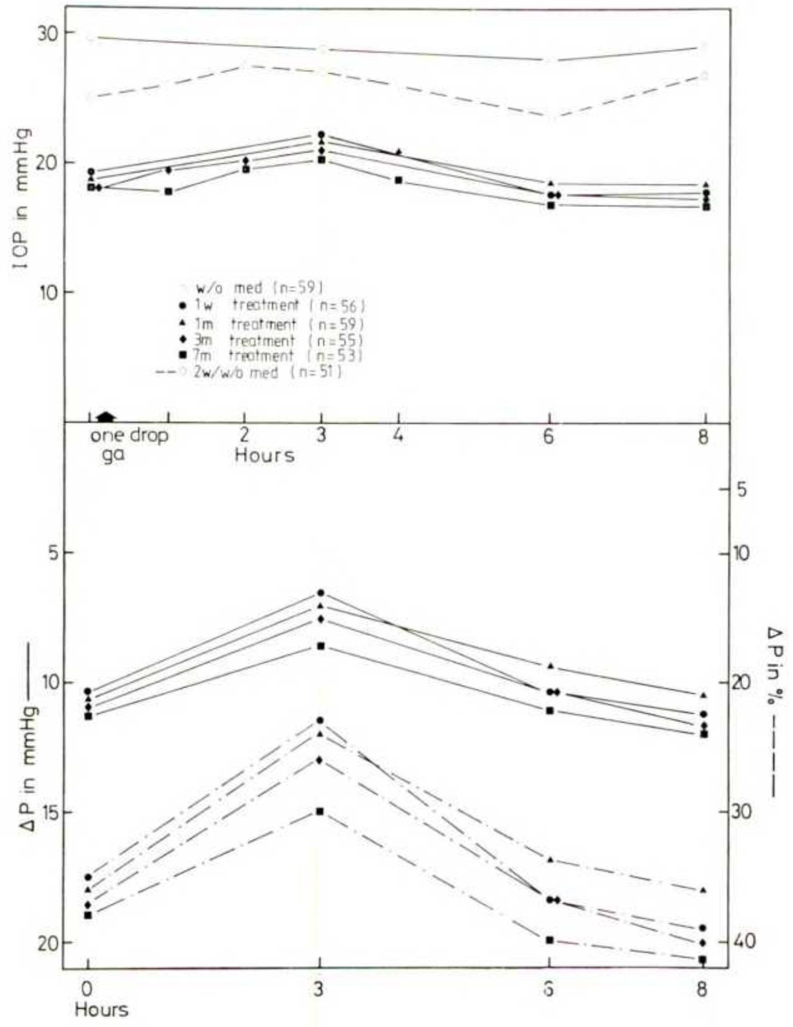

Fig. 1 Upper half: *Mean IOP day-curves of 33 patients with either POAG or suspected glaucoma during treatment (5 patients with additional therapy included)*. Lower half: *ΔP in mmHg (solid line) and ΔP in percentages (dotted line)*

Table 2 *The results of treating 33 patients (59 eyes) with either POAG or suspected glaucoma (5 patients with additional therapy included), in mmHg ± standard error of mean*

	Hours			
	0	*3*	*6*	*8*
Mean IOP in mmHg without medication (n=59)	29·5±0·98	28·9±0·90	27·9±1·08	28·9±1·15
Mean IOP in mmHg after 7 days' treatment (n=56)	19·2±0·69	22·3±0·87	17·6±0·69	17·7±0·82
Mean IOP in mmHg after 1 month's treatment (n=59)	18·9±0·58	21·9±0·67	18·5±0·56	18·4±0·63
Mean IOP in mmHg after 3 months' treatment (n=55)	18·5±0·51	21·4±0·68	17·6±0·57	17·3±0·70
Mean IOP in mmHg after 7 months' treatment (n=53)	18·3±0·60	20·3±0·59	16·8±0·51	16·9±0·52
Mean IOP in mmHg after 2 weeks without medication (n=53)	25·0±0·63	26·9±0·81	23·7±0·78	26·7±0·98

± = standard error of mean.

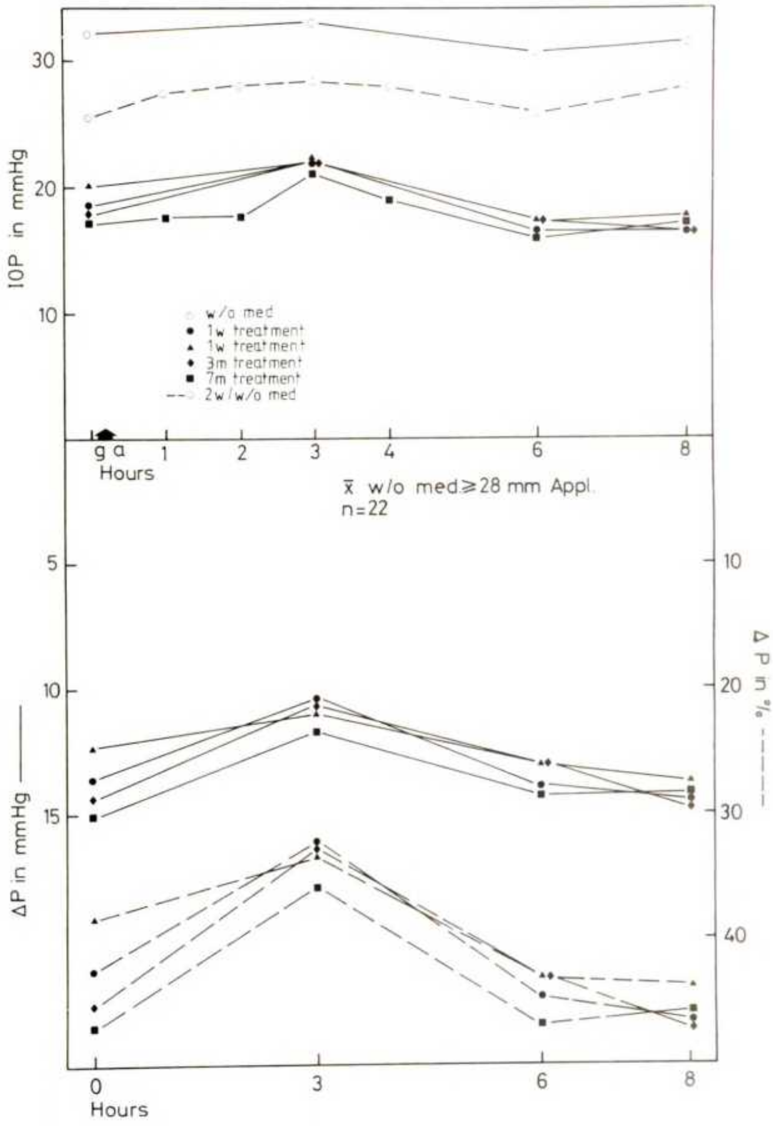

Fig. 2 Upper half: *Mean IOP day-curves of 22 eyes treated only with GA with an average IOP in the day-curve without medication equal to or higher than 28 mmHg*. Lower half: *ΔP in mmHg (solid line) and ΔP in percentages (dotted line)*

curves without medication). Figs 2 and 3 show the results.

There was a striking difference in percentage decrease of IOP. It was 44·6% for the eyes belonging to the group with the higher IOPs and 30·4% for the eyes with the lower IOPs. In Fig. 2 there is a fall in IOP from 31·7 mmHg (average of day-curves without medication) to 17·3 mmHg (average basal level with GA), and in Fig. 3 there is a fall from 24·8 mmHg (average of the day-curves without medication) to 17·2 mmHg (average basal level with GA).

It is interesting to note that, whatever the initial mean IOP was without medication, 24·8 or 31·7 mmHg, there seemed to be a decrease in IOP to a basal limit of 17 mmHg. We do not know the reason for this phenomenon.

The results in the individual patients are shown in Table 3. Twenty-three eyes were well controlled and all had an IOP lower than or equal to 21 mmHg. Twenty-three eyes were controlled and had all IOPs lower than 22 mmHg except at least one peak pressure 3 hours after application in one of the day-curves during treatment. In 14 eyes this peak pressure was lower than or equal to 25 mmHg, and in 9 eyes there were peak pressures between 25 and

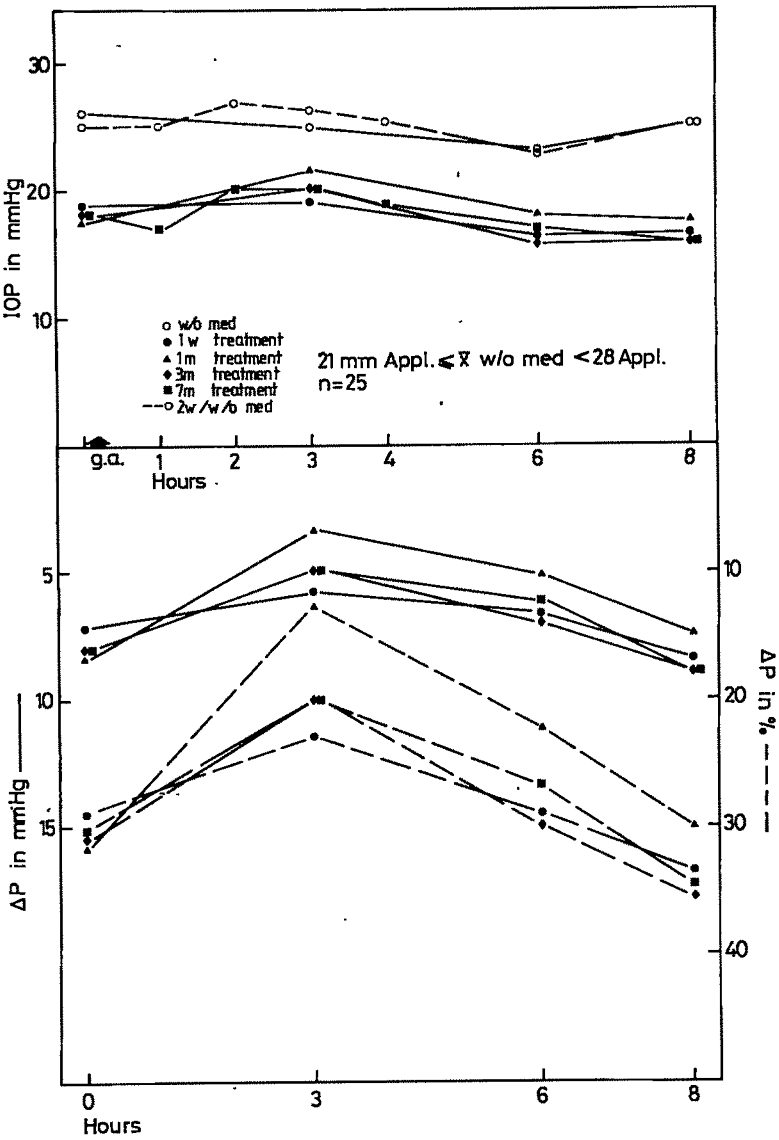

Fig. 3 Upper half: *Mean IOP day-curves of 25 eyes treated only with GA with an average IOP in the day-curve without medication equal to or greater than 21 mmHg and lower than 28 mmHg. The lower half shows ΔP in mmHg (solid line) and ΔP in percentages (dotted line)*

30 mmHg. Nine eyes were not controlled but had a good fall in IOP. In 2 patients (4 eyes) there was no response at all.

Among the patients who were treated with GA alone 46% of eyes had all IOPs lower than 22 mmHg during and after the 7-month period, and 74% had all IOPs lower than 22 mmHg with now and then a peak pressure in a day-curve but not higher than 25 mmHg. The patients who needed additional medication were included in the not well controlled group but with a good fall in IOP. The POAG patient with no response at all, had acetazolamide and pilocarpine 2% 4 times daily as additional therapy. The glaucoma suspect with no response had an initial good response on GA but tachyphylaxis developed.

We compared the results of 12 POAG patients and 9 glaucoma suspects, who were treated with GA alone, with the control level they showed on the previous therapy. The results are shown in Table 4. It indicates that in 18 patients (33 eyes) there was a lower controlling IOP level with GA alone than with previous therapy (3·3 to 3·92 mmHg; $P < 0{\cdot}05$). In 1 POAG patient the level with GA alone

Table 3 *Number of eyes controlled by GA*

	POAG (*n* = *33*)	*Glaucoma suspects* (*n* = *26*)	*Total* (*n* = *59*)
Well controlled	12	11	23
Controlled	14	9	23
Uncontrolled but with decrease in IOP	5	4	9
No response	2	2	4

Table 4 *Mean individual differences in IOP of 21 patients (38 eyes) treated with GA alone with respect to their mean individual IOP on previous treatment; n = number of eyes. For POAG patients the mean number of measurements during previous medication is 12·5 and for glaucoma suspects 14*

	12 POAG	*9 Glaucoma suspects*
Mean lower IOP level in mmHg with GA	–3·92 (n = 15)	–3·3 (n = 18)
Equal mean IOP level with GA	(n = 2)	—
Mean higher IOP level in mmHg with GA	– 0·8 (n = 3)	—

was the same and 2 POAG patients (3 eyes) had a higher pressure with GA alone (0·8 mmHg).

The number of measurements taken during the previous therapy were 12·5 (range 5 to 25) for the POAG patients and 14 (range 7 to 24) for glaucoma suspects. These were measurements taken during examinations at the polyclinic and not when day-curves were done.

SIDE EFFECTS

Only 2 patients found the drops unpleasant and had cosmetic objections. One of these had severe redness of the eye with chemosis and severe ptosis (more than 3 mm). The other had only moderate hyperaemia of the conjunctiva bulbi et tarsi. Fifteen patients with slight redness and 5 with moderate redness of the eyes had no objections to continuing treatment because of this. Transient or slight ptosis (1 to 2 mm) was found in 7 patients and moderate ptosis (2 to 3 mm) in 2. In 2 patients there was evidence of transient keratoepitheliopathy, but this did not lead to interruption of medication. Six patients had reading problems during the first hours after application. In 4 patients (4 eyes) early visual field defects disappeared and in 1 patient with an absolute visual field defect the defect progressed in spite of an excellent response on IOP. Tachyphylaxis was seen in 1 glaucoma suspect after 3 months' treatment. One patient showed serous maculopathy in 1 eye after 1 month's treatment, which disappeared 3 months later after GA was discontinued. She was known to have maculopathy previously. It was not regarded as a side effect but as progression of the underlying maculopathy.

Discussion

Guanethidine is thought to remove the stored noradrenaline in the granulated vesicles of the sympathetic nerve endings, to block the re-uptake, and to cause a depletion of noradrenaline at the nerve ending. As a result hypersensitivity for sympathomimetics develops at the receptor side. Since the Patersons started to use adrenaline in combination with guanethidine many studies on this subject have been done. Until now GA has not yet gained an important place in the treatment of glaucoma. This is partly owing to the side effects and partly owing to unfamiliarity with GA.

We have carried out this detailed study because we believe that more knowledge about its less well known properties was needed. We consider that we have in GA a potential mixture for lowering IOP, though there is some reduction of the effect on IOP 3 hours after application. This reduction is about 3·5 mmHg for the whole group ($P < 0{\cdot}005$). A detailed analysis of this peak effect with GA 3 hours after application will be published elsewhere. The biphasic response during GA treatment has not been previously reported.

In comparison with previous therapy, all patients (except 2 with red eyes) found it pleasanter to administer the drops only twice daily. Hyperaemia of the conjunctivae and slight or moderate ptosis was acceptable to most patients. Visual acuity did not change except in 1 patient known to have progressing cataract. Refraction showed a slight increase in hypermetropia of ½ to ¾ dioptre in 7 patients. After GA was stopped this disappeared. Relaxation of the ciliary muscle may be the cause of it. Reading problems during the first few hours after application of GA disappeared with ½ dioptre stronger presbyopia correction for reading. We do not know whether this is due to widening of the pupil or a slight increase in hypermetropia. Reading problems were mainly in patients aged between 40 and 55. Patients who complained of dark vision with miotics lost these symptoms with GA. Widening of the pupil during the first hours after application was frequently seen.

Summarising, we find that with GA, despite red eyes and slight ptosis, we have an effective conservative treatment for patients with suspected glaucoma and POAG. Younger patients, who had many problems with miotics, respond particularly well on GA. Operations may be delayed in patients who were not responding to previous therapy. Combinations with other conservative treatments are possible.

We gratefully acknowledge the skilful assistance of Mrs J. Loeb, who performed the tonometry, and Mr A. Blijleve, who made the drawings. We thank ZYMA for providing us with Z-15000 PD-70 during the trial.

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British Journal of Ophthalmology, 1979, **63**, 63–66

Ocular and cardiovascular effects of local and systemic pindolol

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SUMMARY Ocular and cardiovascular effects of topical and intravenous pindolol have been studied in a balanced cross-over double-blind trial in 6 healthy volunteers. When applied to 1 eye pindolol lowered intraocular pressure in both the treated and untreated eyes with only minimal reduction in resting pupil diameter and light reflex response. The concentration in plasma was much lower and inhibition of exercise tachycardia about half that when the same dose was administered intravenously. The findings suggest that β-adrenoceptor blocking drugs should not be used in the treatment of glaucoma in patients who also suffer from heart failure.

Pilocarpine has been the mainstay of glaucoma therapy for many years despite the impairment of vision caused by the accommodative spasm and pupillary constriction that accompany its use. The β-adrenoceptor blocking drugs offer a promising alternative to pilocarpine, since they have been reported to control intraocular pressure without impairing visual function (Phillips *et al.,* 1967; Bonomi and Steindler, 1975; Phillips *et al.,* 1977; Leading article, *British Medical Journal,* 1976; Editorial, *British Journal of Ophthalmology,* 1975).

There is, however, a danger that these drugs could exert a systemic effect following local application to the eye because β-blockers are highly lipid-soluble compounds that may pass directly into the circulation or be absorbed after passing down the nasolacrimal duct into the pharynx. The present study with pindolol, a particularly potent β-blocker (Harms, 1976), was designed to test this possibility and to record the pupillary, accommodative, and ocular hypotensive effects that follow its local and systemic administration.

Methods

SUBJECTS

Six healthy persons, 3 male and 3 female, aged 21 to 22 years, volunteered for this study. All had normal visual acuity, light perception thresholds, and ocular tension.

TREATMENTS

Each person attended on 3 occasions, on each of which 4 eyedrops were applied to both eyes and an intravenous injection was given. The eyedrops, delivered with Pasteur pipettes, were of about half the volume given by most commercial droppers. On one occasion pindolol was incorporated to a concentration of 1% in the eyedrops applied to 1 eye; on a second occasion the same total dose of pindolol (1·13 mg) was incorporated in the intravenous injection; on a third occasion no pindolol was given. The solvents for the pindolol sulutions were 0·15 M phosphate buffer pH 6·5 for the drops and 0·9% saline for the injection. Administration of both the drops and the injection was over a 3-minute period. The 3 treatments were given in a complete balanced cross-over design and were administered double-blind.

MEASUREMENTS

Before, and at 0·5-, 1-, and 2-hour intervals after treatment the following were measured in the order given. Intraocular pressure was measured by applanation tonometry under local anaesthesia with benoxinate 0·4%. Three readings were recorded from each eye on each occasion, the tonometer dial being read and reset by an independent observer. Venous blood samples were taken and subsequently analysed for plasma pindolol content by the spectro-

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fluorimetric method of Pacha (1969). The heart rate was measured at rest and during the last 15 seconds of a 4-minute period of exercise on a bicycle ergometer, using an electrocardiographic tracing. The level of exercise (workload 1·5 to 3·0 kiloponds) had been set in a preliminary study to be sufficient to produce an increase in rate of 70 to 120 beats/min, which amounted to a tachycardia of at least 150 beats/min in all but one subject. The near-point of visual accommodation was measured in quadruplicate with a sliding rule (Herxheimer, 1958). The resting pupil diameter and the reflex pupil responses to a train of 0·5-second light flashes at 0·125 Hz were recorded with a Whittaker Series 1800 infra-red television pupillometer (Smith and Smith, 1978). The intensity of the light flashes was arranged to give reflex responses of approximately 1 mm, and the dim background illumination was constant for each experiment.

STATISTICAL ANALYSIS

Measurements obtained before drug administration were subjected to analysis of variance by standard techniques (Snedecor and Cochran, 1967) and found not to differ between experimental occasions. Treatments were therefore compared by analysis of variance of post-treatment measurements only, all treatment times being combined. Correlations between reductions in intraocular pressure or exercise tachycardia and log plasma pindolol concentrations were assessed by analysis of covariance (Snedecor and Cochran, 1967).

Ethical approval for this study was given by the St Thomas's Hospital Research (Endowments) Committee.

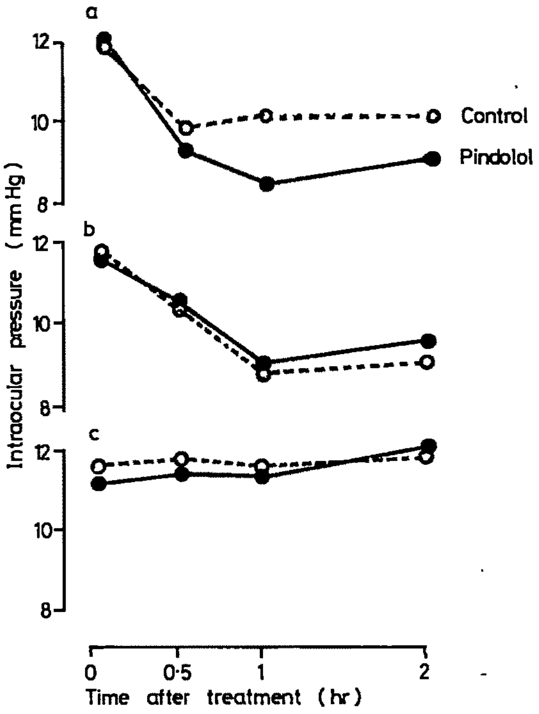

Fig. 1 *Mean intraocular pressure (●—●, treated eye; ○—○, untreated eye) following:* (a) *pindolol 1% (total dose 1·13 mg) instillation into the eye;* (b) *pindolol 1·13 mg intravenously;* (c) *control vehicles*

Results

INTRAOCULAR PRESSURE

The effects of the 3 treatments are shown in Fig. 1. Topical pindolol lowered the pressure in both the treated ($P<0{\cdot}001$) and untreated ($P<0{\cdot}001$) eyes, the fall in the former being greater than in the latter ($P<0{\cdot}01$). Intravenous pindolol lowered the pressure equally in the 2 eyes. By comparison with local administration the pressure fall was less than that produced in the treated eye ($P<0{\cdot}001$) and equal to that in the untreated eye.

OTHER EYE SIGNS

Pupillography showed that topical pindolol reduced the resting pupil diameter and the amplitude of the light reflex of the treated eye only to a very small, though statistically significant (diameter $P<0{\cdot}001$; reflex $P<0{\cdot}01$), extent. The mean changes in diameter ($<0{\cdot}6$ mm) and reflex response ($<0{\cdot}15$ mm) were imperceptible to observers by simple inspection of the eye. No change followed intravenous pindolol. Visual accommodation was unaffected by any treatment.

HEART RATE

The effects of the 3 treatments on resting heart rate and on exercise tachycardia are shown in Fig. 2. Both ocular and systemic pindolol reduced resting heart rate and inhibited exercise tachycardia. The reduction in resting heart rate was small (mean change less than 7 beats/min) both with ocular ($P<0{\cdot}05$) and with intravenous ($P<0{\cdot}05$) administration. The exercise-induced increase in rate was inhibited 12·6% by ocular pindolol ($P<0{\cdot}05$), 25·6% by intravenous pindolol ($P<0{\cdot}001$).

PLASMA PINDOLOL CONCENTRATION

The findings are given in Table 1. After ocular instillation pindolol was detectable in plasma within 30 minutes, but the concentrations found were substantially lower than after intravenous injection at all times ($P<0{\cdot}001$). To investigate the dose response relationship for inhibition of exercise

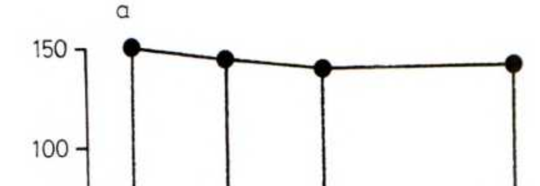

Fig. 2 *Mean heart rate at rest (lower line) and after exercise (upper line) following:* (a) *pindolol 1% (total dose 1·13 mg) instillation into the eye;* (b) *pindolol 1·13 mg intravenously;* (c) *control vehicles*

tachycardia and for reduction of pressure in the untreated eye, correlations were sought between the magnitude of these effects and log plasma concentration (intravenous and local administration). In this analysis 5 data points were excluded because the pindolol concentration was below the limit of detection. It was found that whereas the cardiac response correlated with log plasma concentration (r = 0·752, P < 0·001) the ocular response did not (r = 0·179, P > 0·05).

Table 1 *Plasma pindolol concentration (µmol/l) (mean ± SD)*

	Time (hr)		
Route of administration	*0·5*	*1*	*2*
Ocular instillation	2·4 ± 3·2	6·8 ± 2·8	3·2 ± 3·2
Intravenous	29·8 ± 6·4	34·2 ± 9·3	27·0 ± 9·3

Discussion

Local and systemic pindolol caused ocular hypotension in these normal subjects without impairment of visual function. There was no effect on accommodation, and the small decrease in resting pupillary diameter and light reflex amplitude found after local administration was clinically insignificant. The direction of these small pupillary changes, which resemble those seen with low doses of cholinomimetic drugs (Smith and Smith, 1978), is consistent with the hypothesis that there is a small population of β-adrenoceptors on the human sphincter pupillae which mediates relaxation of this muscle during sympathetic dilatation of the pupil (Kern, 1971).

This study has revealed a potential drawback to the use of β-blockers in glaucoma in that there was sufficient absorption of pindolol from eyedrops to cause partial blockade of cardiac adrenoceptors. It is possible that lower doses might control pressure adequately with less chance of systemic side effects, but this finding does suggest that β-blockers should not be given to glaucomatous patients who also suffer from cardiac failure or, in the case of non-cardioselective blockers, from bronchial asthma.

In this study the cardiac β-blockade that followed local administration of pindolol resulted in a decrease in resting heart rate and a reduction of exercise tachycardia that was nearly half the size of the reduction obtained after intravenous injection of the same dose. This systemic effect was still present when the last reading was taken at 2 hours after application of the drops. The reduction of exercise tachycardia that followed intravenous pindolol and its correlation with plasma drug levels is in agreement with previous studies (Hicks *et al.*, 1972; Gugler *et al.*, 1975). However, the effect of pindolol on resting heart rate, though always small in magnitude, appears to be variable in direction, some authors reporting a decrease (Gugler *et al.*, 1975) as found in this study, whereas others (Hicks *et al.*, 1972) report an increase. These differences may be related to the partial agonist activity of this particular β-blocker acting on patients in variable basal conditions.

It was interesting to find that pindolol treatment of 1 eye resulted in a pressure fall in the contralateral untreated eye. Although it is possible that this resulted from systemic absorption of the drug, such an explanation seems unlikely, because the contralateral fall occurred in the presence of far lower plasma concentrations than were present after intravenous administration, which gave a comparable reduction in pressure. Other workers have reported a similar reduction in the contralateral eye after local timolol (Zimmerman and Kaufman, 1977) and pilocarpine (Willetts, 1969) treatment. Further, a pressure reduction produced simply by pressing on 1 eye to increase venous drainage of aqueous is also accompanied by a fall in the opposite eye (Prijot and Stone, 1956). Possibly there exists a regulatory mechanism whereby pressure in both eyes is maintained at a similar level.

Financial support for this work was provided by the Medical Research Council and Sandoz Products Ltd. We are grateful to Dr W. L. Pacha of Sandoz (Basle) for the pindolol assays.

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Book reviews

The Pathogenesis of Nerve Damage in Glaucoma: Contributions of Fluorescein Angiography. By GEORGE L. SPAETH. 1977. Pp. 160, figs., tables, refs. Grune & Stratton, New York (£13·85)

The changes in the optic nerve head in glaucoma have usually been explained in terms of either a mechanical or a vascular hypothesis. According to the latter, raised intraocular pressure reduces blood flow through the optic nerve head and the changes which occur are to be regarded as due, at least in part, to ischaemia. Experimental work over the past 10 years has tended to support the vascular hypothesis of glaucomatous damage to the optic nerve, and during a similar period of time there have been great advances in the technique of fluorescein angiography. The practising clinician may well ask, therefore, whether fluorescein angiography will help him in the diagnosis and in the management of glaucoma, and as a matter of more academic interest he may want to know how far fluorescein angiography has advanced our understanding of the basic causes of this disease. All the basic information can be obtained from the journals, of course, but the papers are numerous and some of the results are, not unexpectedly, contradictory. In this book Dr George Spaeth has presented a review of much of the work on glaucoma using fluorescein angiography and other techniques of assessing the vascular circulation in the eye, with an understandable emphasis on his own painstaking and extensive studies. He has tried, from this mass of material, to extract useful answers to the sort of questions mentioned above.

With regard to the experimental approach he points out that many investigations have been concerned with acute transient elevations of intraocular pressure, which may have some bearing on acute closed-angle glaucoma but do not necessarily help to elucidate the causation of changes in chronic simple glaucoma. In general it is clear that fluorescein angiography reveals significant differences in the blood flow through the optic nerve head between patients with chronic simple glaucoma and normal subjects. There are, however, several patterns which can be recognised within the group of glaucoma patients, and this consideration leads Dr Spaeth to put forward a tentative classification into 4 types of glaucoma. In primary hyperbaric glaucoma neuronal damage is directly due to raised intraocular pressure. In primary ischaemic glaucoma the damage is due to ischaemia, which is not, however, related to the elevation of intraocular pressure. In secondary ischaemic glaucoma the elevation of intraocular pressure brings about ischaemia, which causes the damage. In the fourth type of glaucoma there is a mixture of these mechanisms. It is claimed that fluorescein angiography would help the clinician to discover the predominant mechanism of damage in the individual patient. Nevertheless, the conclusion reached is that it will not be practicable to use the current technique of fluorescein angiography on a large scale in the diagnosis and management of glaucoma.

Such is the scope of this book. It is an interesting, important, and thoughtful review of the problem with a detailed analysis of numerous fluorescein angiograms and other investigations, and is recommended to all who have a particular interest in glaucoma. J. GLOSTER

Intraocular Tumors. By GHOLAM A. PEYMAN, DAVID J. APPLE, and DONALD R. SANDERS. 1977. Pp. 382, figs., tables, refs. Appleton-Century-Crofts, New York (£19·95)

The participants in a symposium on intraocular tumours held at the University of Illinois Eye and Ear Infirmary in Chicago recently have combined with other authorities on the subject to produce a valuable and up-to-date book dealing with all aspects of intraocular neoplasms. The editors have taken full advantage of the expert knowledge at their disposal, and all of the contributors have been lavish with the references at the end of each chapter. Apart from a single author from West Germany, the volume is entirely the work of individuals based in the United States.

The book is short enough to be read with advantage by advanced students and is sufficiently comprehensive to be used as a standard reference work. The prominence given recently to the need for improved diagnosis in intraocular malignant disease, particularly with reference to melanoma of the choroid and retinoblastoma, has been emphasised. Full consideration is given to clinical diagnostic methods, to specialised techniques such as fluorescein angiography and ultrasonography, and to immunological advances in tumour diagnosis and treatment.

The benefits to a patient with a malignant melanoma of the choroid consequent upon enucleation are to some ophthalmologists questionable, and a reasoned approach to this important problem is made. The necessity for distinguishing between primary and secondary choroidal malignancy is always present, and modern developments in diagnosis are objectively assessed. The initial diagnosis of retinoblastoma is of equal consequence, and here again the editors have assembled up-to-date information concerning this tumour. Particularly helpful chapters deal with recent advances in the study of retinoblastoma and with current concepts in its treatment.

The volume is one which should find a place in the libraries of postgraduate institutions and in the personal libraries of ophthalmologists specialising in retinal diseases. J. R. HUDSON

Advances in Ophthalmology. Vol. 36. Edited by M. J. ROPER-HALL and E. B. STREIFF. 1978. Pp. 254, figs., tables, refs. Karger, Basel (DM188)

The 36th edition of the series 'Advances in Ophthalmology' is a commemorative volume in honour of Professor E. B. Streiff. The book follows the traditional form of this series, with a number of contributions on a variety of subjects from European authors. In all there are 28 articles, of which 11 are in English, 11 are in

French (4 with short English summaries), and 6 are in German (2 with short English summaries). The scope of the papers is wide, with an agreeable mixture of clinical and scientific contributions; there are in addition several case reports and an article on ophthalmic history.

In a composite volume such as this it is difficult to single out any particular contribution for special mention, but the high quality of the illustrations throughout should be stressed. Professor Streiff's long association with Lausanne has stimulated a number of articles from Swiss authors, and English readers might be put off by this apparent parochialism, but the uniform standards of this popular series are maintained. T. J. FFYTCHE

Insights from the Blind. By SELMA FRAIBERG. 1977. Pp. 297, figs., tables, refs. Souvenir Press, London (£5)

This book is the detailed investigation of a number of children who were born blind and who had no other disability. The development of grasping, standing, mobility, prehension, and speaking is recorded. It is apparent that it is important to organise an educational programme which is based on the principles of developing the blind child as an individual and making him recognise this individuality. The book will be of the greatest interest to those who have to work with blind children. A. G. CROSS

Der Augenarzt. Vol. 5. Edited by KARL VELHAGEN. 1978. Pp. 893, figs., tables, refs. George Thieme, Leipzig (DDR248)

Volume 5 of 'Der Augenarzt' edited by Karl Velhagen takes the form of previous volumes in this series, with 6 contributions on a variety of topics. Each chapter is virtually a short textbook, examining the subject in depth and providing a comprehensive bibliography, so that the book is both a teaching manual and a source of reference.

The opening chapter discusses ocular trauma and its management and prevention. This is followed by a short illustrated lecture on the biomicroscopy of the peripheral retina. Professor Vodovozov discusses the technique and findings of ophthalmochromoscopy, a method of examination that has never received much interest in Britain. It is unfortunate that the fundus appearances in this type of investigation are displayed by diagrammatic paintings rather than photographs. There is a comprehensive treatise on radiotherapy of the eye and orbit, followed by a short section on ocular physiotherapy, which includes some unusual and exotic forms of treatment not readily available under the NHS. The final chapter is the longest and deals with disorders of ocular motility. It discusses the physiology of binocular vision together with disturbances of ocular position and motility and abnormalities of lid function.

Like its predecessors, this book will appeal to postgraduate and practising ophthalmologists, and if it were available in English translation the sections on trauma, radiotherapy, and ocular motility would be essential reading for those studying for diploma and fellowship examinations. T. J. FFYTCHE

International Guide to Aids and Appliances for Blind and Visually Impaired Persons. 1977. American Foundation for the Blind Inc., 15 West 16th Street, New York, New York 10011 ($3·00)

This is the second edition of a standard reference book on the management of severe visual defects. The first edition was called the *International Catalogue of Aids and Appliances for Blind and Visually Impaired Persons.* It is comprehensive but not complete and provides a general picture of the devices available. The guide has information about all Braille equipment, sound equipment like talking-book machines and tape recorders, clocks and watches for the visually handicapped, mobility aids, and calculators. There are also details about educational and occupational aids and about low-vision aids. Devices are described to help in cooking, measurement, music, handwriting, typewriting, and telephoning. Help with games, sports, and puzzles is also available. It is a most useful volume for the visually handicapped and those who work with them. A. G. CROSS

Dialogues in Ophthalmology. Vol. 1. Diagnosis and Management of Open Angle Glaucoma. Edited by PAUL HENKIND. 1977. Pp. 58, 3 cassette tapes. Harper & Row, Hagerstown, Maryland ($42·50)

Dialogues in Ophthalmology is a collection of 3 cassette tapes and an accompanying booklet. Both carry a discussion between the moderator, Paul Henkind, and 3 experts, on the diagnosis and management of open-angle glaucoma. The discussion is ably led by Dr Henkind, passing in a clear and logical manner from definition to diagnostic signs and then to the timing and type of treatment to consider in the management of the disease. This discussion, containing many practical points and pearls of wisdom, would be useful both for residents preparing for the Fellowship and for general ophthalmologists wanting to update their knowledge. I found it more convenient to listen to the discussion than to read the exact transcription. It might have been more useful to condense the information on the tapes for presentation in the booklet. If the points made could have been given references, many of them would have been lifted above the level of anecdote. This work deserves a wide public, though it is not necessarily an item to purchase for constant reference. R. HITCHINGS

Discussions on Glaucoma. Proceedings of the 1975–76 Symposia on Open and Closed Angle Glaucoma sponsored by the National Society for the Prevention of Blindness. Edited by PAUL R. LICHTER and DOUGLAS R. ANDERSON. 1977. Pp. 156, figs., tables. Grune and Stratton, London (£11·35)

This book is a report of two symposia sponsored by the National Society for the Prevention of Blindness in the USA in 1975 and 1976. Each symposium takes the form of case presentations by one of the coauthors to a panel of specialists before an invited audience. Paul Lichter introduces the 12 cases of open angle, congenital, and secondary glaucoma, which constitute the subject of the first meeting, and Douglas Anderson is the moderator of the second meeting, consisting of 7 cases of angle closure glaucoma. The panels consist of eminent researchers into glaucoma and are different in each symposium (except for Robert Shaffer, who was present in both, and whose comments are always to the point, profound yet essentially practical). The case presentations are halted at certain points for discussions and generalisations, and much ground is covered. The bias of the symposium is towards the solution of specific everyday problems, and, not unexpectedly, the level of discussion varies widely between traditional views and controversial and stimulating statements.

It is clearly impossible to discuss the 19 chapters individually, but perhaps a few statements and opinions may be singled out for their interest. Assessment of the diurnal variations in pressure is best carried out by sporadic checks at the clinic at different hours, or by home tonometry; inpatient hospital phasing is not so reliable, as it involves a profound change in the patient's routine. Almost all the panelists commonly used the water drinking test, but tonography is no longer a routine investigation, being reserved for special cases. A recent spate of litigation cases in the US concerning juvenile glaucoma prompts several panelists to perform tonometry on every co-operative subject regardless of age. However, Shaffer would limit this to cases with suspicious-looking discs and to those persons in whom it can be carried out in a reasonably short time.

Epinephrine almost certainly improves outflow facility fairly rapidly and not, as was thought, after a long latent period. The peak of its dose-response curve appears to be at the 1% concentration of active drug in the short term, though it may be as high as 2% in the long term (Bernard Becker). Stability of adrenaline solution is greater with the bitartrate and the hydrochloride (Epifrin, Glaucon) than with the borate (Epinal, Eppy), but the borate compounds are more comfortable to use. Although little statistical evidence has been adduced, there is an impression that the disc cup changes more readily if it is already large (John Hetherington). In ocular hypertension the pressure responses to, and patient tolerance of, treatment are important factors in deciding when and how much to treat. In drainage operations vitreous aspiration is increasingly recommended to prevent sealing up of the drainage aperture by vitreous. Provocative tests in angle closure glaucoma remain essentially unreliable. The least unsatisfactory tests are the dark room test and the prone test. Mydriatic tests give many false positives. Neither the patient's advanced age nor a considerable degree of widening of the angle with pilocarpine should weaken our resolve to operate on every case of acute angle closure glaucoma (Pollack). However, tonography has a place in evaluating the chances of success of peripheral iridectomy after an acute attack: if $C \leq 0{\cdot}1$, we can expect over 75% of failures (Shaffer).

The volume is beautifully presented and contains several illustrations and clear tables. JOHN ROMANO

Mechanisms of Colour Vision. By W. S. STILES. 1978. Pp. 287, figs., tables, refs. Academic Press, London (£14)

This book contains some of the important papers published during the last half century by Dr W. S. Stiles, a doyen amongst visual physicists. The title is slightly misleading, because the author's wide erudition has enabled him to range not only over the mechanisms of colour vision but also over those of vision in general. The papers are reproduced photographically, and in an introductory chapter there is an indication of the extent to which the author may have wished to modify earlier views. Some of the papers may be hard to trace in the original, and for this reason newcomers to the field have every reason to be grateful for the appearance of the book. Its method of production, however, entails repetition, and this may cause a justifiable grumble on economic grounds. R. A. WEALE

Correspondence

On difficulties in deciding the aetiology of cataract

TO THE EDITOR, *British Journal of Ophthalmology*

SIR, Because the lens fibre system contains only 1 type of cell it has a fairly limited number of ways in which it can respond to injury and on interference with its nutrition. It is therefore extremely difficult from the appearance of the cataract, and the clinical examination of a few cases, to decide whether a history of exposure to a known cataractogenic agent is proof that this agent is important in the genesis of cataract in man, as has been implied, for instance, in the recent study by Zaret and Snyder (1977).

As an example of such a difficulty we may consider a patient employed in servicing radar equipment who had a history of intermittent exposure over a period of 20 years to 3-cm microwaves from high-intensity sources of up to 60 kW. He developed cataract at the age of 52 with reduced vision in each eye. Slit-lamp examination showed interesting features in both lenses. There was vacuolation of the anterior capsule and striate changes in the anterior cortex, while at the posterior pole there were vacuoles and a feathered appearance of lens fibres. No other changes in the eye were apparent, and the intraocular tensions were normal.

It was possible at a later date to examine these lenses by light and electron microscopy. There were large areas of fibre disruption at the anterior pole, and portions of the anterior epithelium appeared to have suffered some necrosis. In addition the superficial cataractous lens fibres were separated from the capsule by clefts filled with albuminous fluid. At the posterior pole the lens fibre membranes had produced myeloid whirls and numerous granular bodies. From these appearances, which can all be seen in senile cataract, it was not possible to state that the changes were characteristic of microwave cataract. This was so despite the initial somewhat unusual slit-lamp appearance.

It would seem, therefore, that to establish beyond reasonable doubt that, for example, microwave radiation is significant in the production of cataract in human subjects it will be necessary to perform a controlled study of patients which have been exposed to this hazard and matched for age to those not so exposed.

Some statistical considerations along these lines also have a bearing on the problem of attributing causation in the absence of a demonstrable noxious stimulus. In view of the relatively young ages of the cataract patients considered by Zaret and Snyder (1977) one has to face the question whether a non-avionic aetiology is statistically defensible. Before any of the necessary assumptions is dismissed out of hand it may be as well to suggest that such an analysis would have been expected in the original paper on the ground that an explanation on an avionic basis would in any case have to stand up to an epidemiological comparison on an age-for-age basis, as suggested above.

We have to form an estimate of the number of cataracts, C, in different age groups in a defined population. According to Van Heyningen (1975) this is about five times greater in the USA than values appropriate for the United Kingdom and Israel (Caird, 1973). It is easily shown from those studies that, for ages younger than 70, the relation between C and age, A, is given approximately by

$$\log C + 5{\cdot}8 = 0{\cdot}048\,A \qquad (1)$$

In other words, with a 1:10 chance of a cataract extraction at the age of 100 this drops by a factor of 250 at the age of 50. The age distribution of New York approximates to the rectangular type of reasonably healthy modern urban populations (Money, 1973), that is, the fraction, S, of people in the various age groups are approximately equal within the average life span. The latest figures available for New York's population distribution are dated 1974, and the 30 to 40 band is somewhat narrow, at 10% owing to the first world war period. The population, P, of New York is approximately $1{\cdot}2\times10^7$, and the number, S, of ophthalmic surgeons in that city 250. The mean number of cataract extractions per annum per surgeon (in a given age group) is

$$a = C_p\ P/S \qquad (2)$$

It will be recalled that the value C is to be multiplied by a factor f, estimated to be 5, to give values appropriate to New York. For the age group 30 to 40, $C \approx 4 \times 10^{-4}$ and $p \approx 0{\cdot}10$.

Substitution into equation (2) gives $a = 0{\cdot}96$. This is an average value per surgeon per year for the age group of 30 to 40.

However, patients do not arrive as fractions, and one has to ask oneself about the probability of seeing none, 1, 2, 3, 4, etc. As these events are mercifully rare, the calculus of Poisson sums is applicable. According to this (*cf.* Davson, 1976), the probability of an event occurring 0, 1, 2 . . . m times when its average occurrence is a, is given by $\Pi_m = (a^m/m!)e^{-a}$. Thus for $m = 0$, $\Pi = 0{\cdot}38$, or the chance of not getting such a patient any one year is 2:5. Similarly, the chance of getting just 1 is 0·37, or 1:3; and that of getting 2 is 0·18, or 1:5. In other words the chance of getting at least 1 patient in the above age group is 0·63:1 in 1 year or 2 in 3 years.

Now these values are clearly high odds in our context and kept low by the assumption that all New York surgeons have an equal chance. If British surgeons are anything to go by, specialisation takes place within the field, and this means that the chances of those interested in the matter are going to be correspondingly increased.

Insufficient information is available to enable one to allow for the fact that the data on cataract statistics vary in their specificity. While, as pointed out earlier, Zaret and Snyder have provided evidence for the existence of cataracts observed also in radiation environments, they have omitted to provide an estimate of dosages, exposure times, etc., and also omitted to apply probability calculations whereby to test the statistical validity of their conclusions. The above estimate does not rule out their opinion. On the other hand, an application of the t test to the appropriate Poisson data shows that, to render the conclusion of the above authors valid, the incidence of so-called avionic cataracts would have to be greater by almost an order of magnitude for one to be able to establish a significant relation between them and unspecified radiations.

R. F. FISHER
R. A. WEALE

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Notes

Computers in ophthalmology

A course in application of computers to the care of ophthalmic patients and in clinical research will be held on 5–6 April 1979, in St. Louis, Missouri. For further information contact Robert Greenfield, DSc., Biomedical Computer Laboratory, Washington University School of Medicine, 700 South Euclid Avenue, St. Louis, Missouri 63110, USA.

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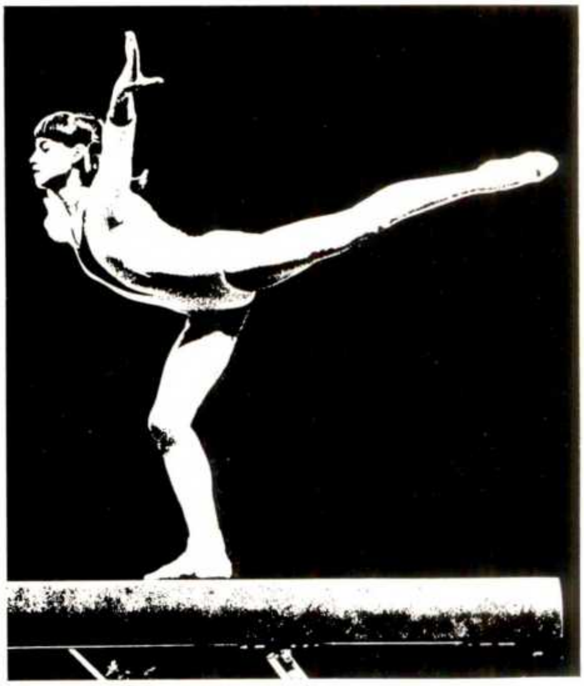

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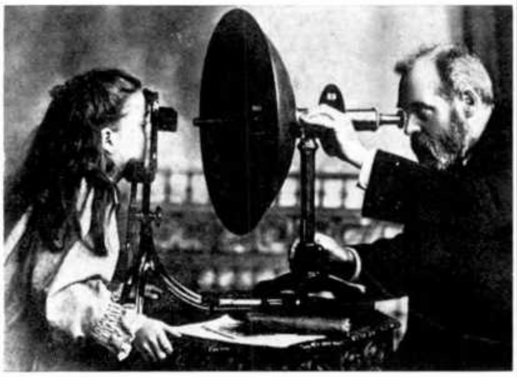

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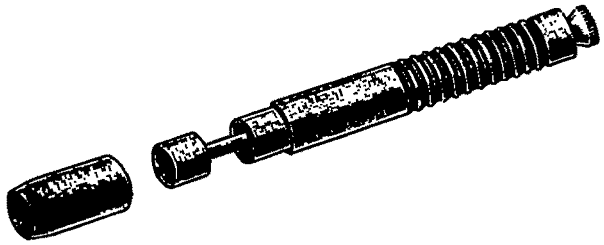

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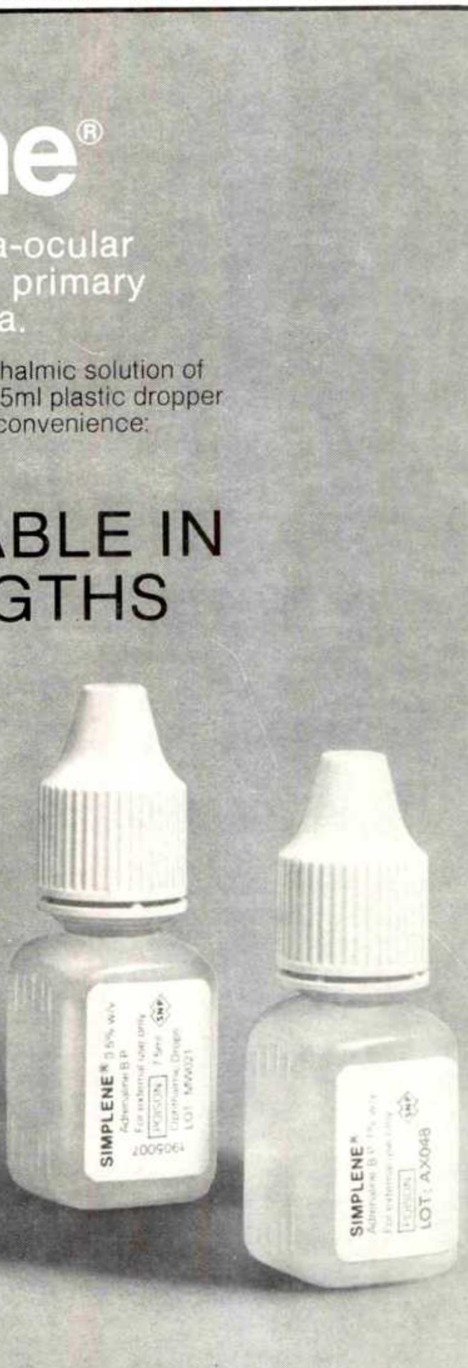

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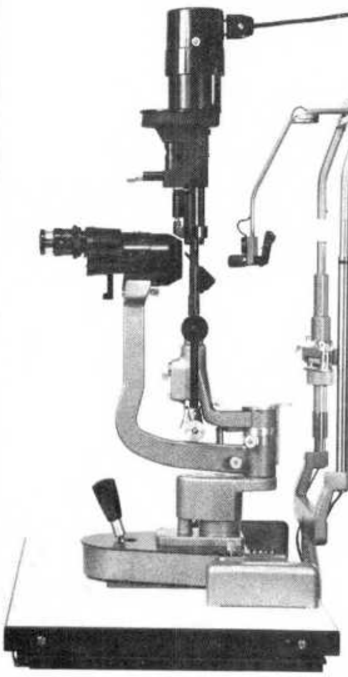

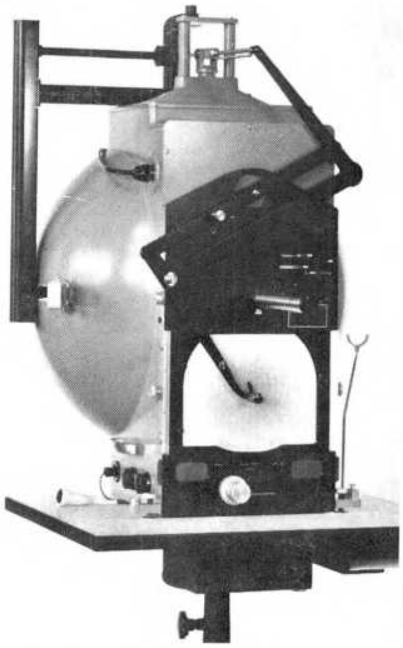

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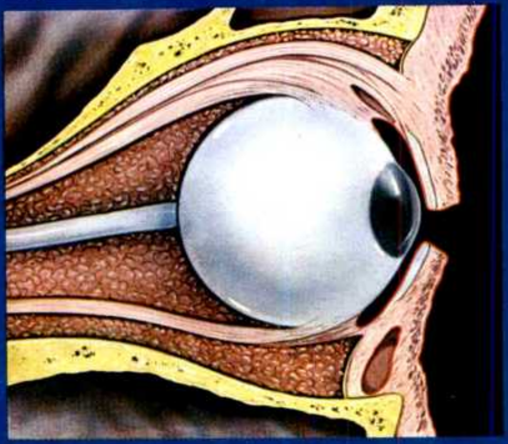

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British Journal of Ophthalmology, 1979, **63**, 71–84

The retinal-pigment epithelial interface

WALLACE S. FOULDS

From the Tennent Institute of Ophthalmology, University of Glasgow

SUMMARY The interdependence of the outer retina and pigment epithelium is illustrated by the functional changes and structural alterations which occur in each in response to choroidal ischaemia, retinal detachment, vitamin A deficiency, and other causes. The pluripotential role of the pigment epithelium is stressed, particularly in relation to the phagocytosis of outer segment material and the ability of this layer to undergo metaplasia into a variety of different cell types. Similarities of all disturbances of the retinal-pigment epithelial interface to retinitis pigmentosa are pointed out, and the significance of the findings in relation to this disease is discussed.

To see at all we must of course possess a light-absorbing structure to carry out the energy conversion required to initiate the visual impulse. In almost all species this structure takes the form of a specialised light-sensitive layer of neural tissue derived from the primitive neuroectoderm. In man the eye first forms as an outpouching of the primitive forebrain at a very early stage of development to form a cavity, the primary optic vesicle being lined with ependymal cells. This cavity is obliterated by invagination and the formation of the secondary optic vesicle or optic cup, and it is the acquired juxtaposition of the anterior and posterior hemispheres of the optic vesicle with which I shall deal (Fig. 1).

Early development

At a very early stage in development the posterior half of the cup becomes pigmented and forms the retinal pigment epithelium, which, though in some respects a very specialised tissue, in others remains primitive, for the retinal pigment epithelium throughout life is capable of expressing itself in the pluripotential fashion usually associated with more primitive types of cellular activity. It is interesting that in the developing eye the layer of primitive pigment epithelium is many cells thick, whereas in the adult it is monocellular. Mitotic division of retinal pigment epithelial cells is not seen in the adult, and it may be that after embryogenesis is complete, no further pigment epithelial cells are formed. The same may be true of the pigment itself, for adult pigment epithelial cells lack the enzyme systems needed to produce pigment, so that embryonic synthesis of pigment may be a once-for-all event on this tissue (Feeney, 1973b, Berman *et al.*, 1974).

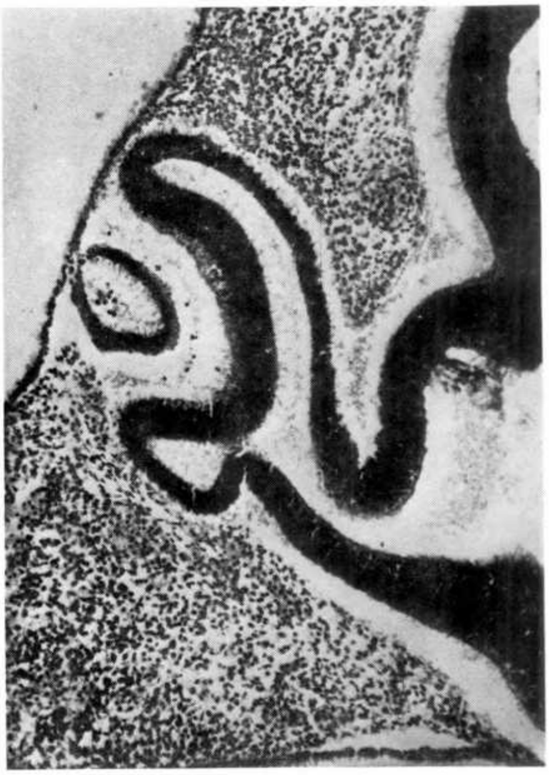

Fig. 1 *The optic cup in a human embryo to show acquired juxtaposition of anterior and posterior hemispheres of the optic vesicle*

Experimentally it has been shown (Coulombre,

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1965) that contact between the developing retina and pigment epithelium is necessary for maturation of the pigment epithelium, for if the 2 layers are separated the primitive pigment epithelium proceeds to develop into a neuroretina. This inhibition of the pigment epithelium by contact with the overlying retina is of interest in relation to the behaviour of the pigment epithelium in the adult eye.

The ciliated ependymal cells of the optic vesicle eventually develop into the receptor cells of the retina and give rise to the other retinal layers, and even in adult life the remains of cilia can still be discerned in the receptor cells.

Although the juxtaposition between the retina and the pigment epithelium is an acquired one, it is physically very close. The outer retina and the inner aspect of the pigment epithelium interdigitate, and the outer segments of the receptor cells fit closely between the apical processes of the pigment epithelial cells to form a near union which undoubtedly has mechanical strength (Foulds, 1975) but which, more importantly, brings a large surface area of pigment epithelium into close proximity with an extended surface area of outer retina. This arrangement allows easy transfer of metabolites and waste products between the 2 cell layers. It is the importance of this close contact that I wish to stress and the consequences of disturbance of this anatomical and physiological relationship.

Structure and function

Before doing so it is necessary to outline further some structural and functional aspects of the 2 layers. Physically any small gaps between the apical processes of the pigment epithelial cells and the outer retina are filled with a mucopolysaccharide ground substance, the interphotoreceptor matrix (Sidman, 1958; Zimmerman and Eastham, 1959; Fine and Zimmerman, 1963; Rohlich, 1970; Feeney, 1973a), which shows well when stained with colloidal iron and the Prussian blue reaction (Fig. 2). As Berman and others have shown (Berman, 1969; Berman and Voden, 1970), this material is different from the hyaluronic acid of the cortical vitreous, for it is not depolymerised by hyaluronidase as is the vitreal mucopolysaccharide.

The function of the interphotoreceptor matrix is not known. Speculatively it has been suggested that it may be an ion trap maintaining local concentrations of various ions which may be concerned with the initial generation and transmission of the visual impulse in the outer segment of the receptor cell. It does not seem to act as a tissue glue holding the retina in place, for it is apparently normal in eyes with retinal detachment (Fig. 3). An intriguing

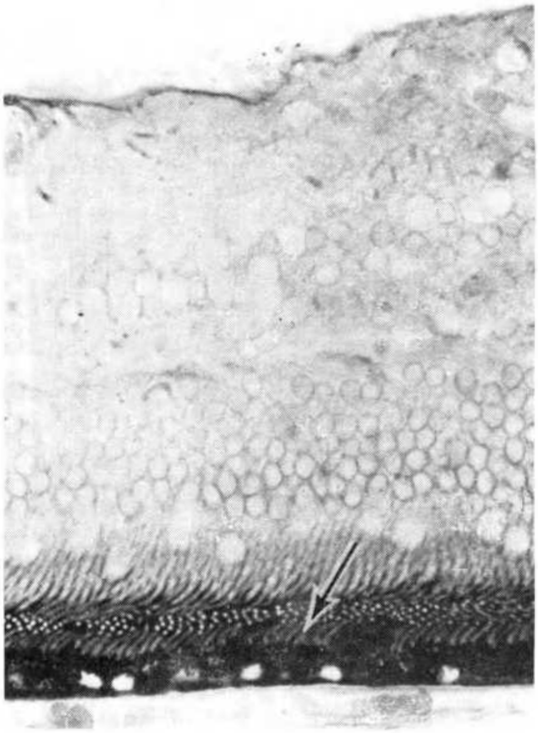


Fig. 2 *Human retina stained with Prussian blue reaction to show the interphotoreceptor matrix (arrowed)*

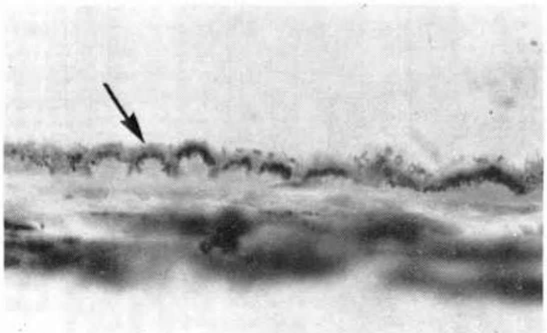


Fig. 3 *Rabbit pigment epithelium in experimental retinal detachment to show interphotoreceptor matrix material on pigment epithelial surface (arrowed)*

possibility is that it may act as a damping mechanism preventing damage to the outer segments by shearing movements of the retina in relation to the pigment epithelium, for the connection between the outer and inner segments of the receptor cell is very thin, and one could imagine that shearing movements could easily damage the connecting structures if they were unsupported.

The origins of the interphoto-receptor matrix are also disputed. If one examines tissue in which the receptor cells have degenerated, after experimental retinal detachment, for example, one can see a heavy concentration of mucopolysaccharides on the apical surface of the pigment epithelial cell layer and on the now distantly situated Muller cell surface, suggesting perhaps that each of these cell types is capable of elaborating the interphoto-receptor matrix (Johnson and Foulds, 1976).

Another aspect of the pigment epithelium is its ability to phagocytose material presented to its inner surface. Not only does it scavenge the potential subretinal space, it is actively concerned in the continuous phagocytosis of the outer limbs of the retinal receptors, both rods and cones (Bairati and Orzalesi, 1963; Young and Bok, 1969).

This phagocytosis is part and parcel of the cycle underlying the degradation and regeneration of visual pigment, a cycle which appears to operate at several levels. There is a molecular level involving the reversible isomerisation of retinol, and a much grosser level involving the physical breaking down of the outer segments, their subsequent metabolism in the retinal pigment epithelial cell, and presumably the re-use of the breakdown products by the receptor cells once again. Whether all the breakdown products of phagocytosis are recycled to the retinal receptor cell is a moot point. It has been suggested that some of the material may be transported across Bruch's membrane and account for the accumulation in it of basophilic material which may represent an early stage in the development of senile disciform degeneration of the macula (Hogan, 1971).

Certainly under some circumstances, for example induced choroidal ischaemia, phagosomes from the pigment epithelium may be found in the endothelial cells of the choroidal blood vessels, but this is almost certainly a very artificial and pathological situation (Johnson, 1975b).

The capacity of the pigment epithelium to ingest outer segment material appears to be very much greater than the basic requirement, and where there is an increased breakdown of outer segments the phagocytic activity of the pigment epithelium may also be greatly increased. Recently it has been shown that in some species pigment epithelial phagocytosis undergoes a circadian rhythm, being greater during the day than at night (Le Vail, 1976). A sudden increase in ambient illumination after a period in the dark also results in a rapid increase in phagocytic activity in the pigment epithelium (Bassinger *et al.*, 1976).

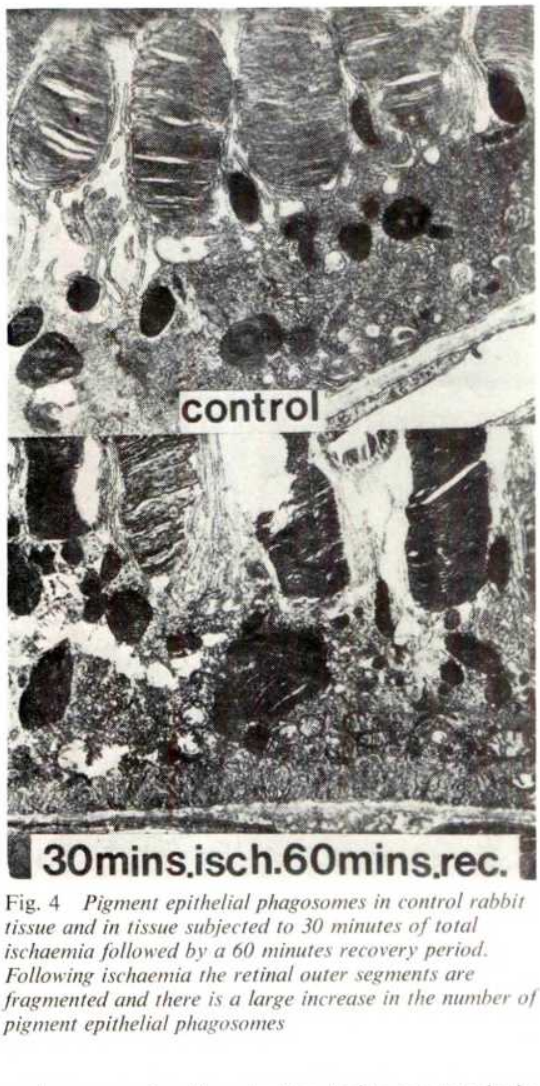


Fig. 4 *Pigment epithelial phagosomes in control rabbit tissue and in tissue subjected to 30 minutes of total ischaemia followed by a 60 minutes recovery period. Following ischaemia the retinal outer segments are fragmented and there is a large increase in the number of pigment epithelial phagosomes*

A pathological increase in outer segment breakdown will also be followed by an increased rate of phagocytosis in the pigment epithelium. Thus, for example, choroidal ischaemia in the rabibt causes a rapid breakdown of the receptor cells and particularly their outer segments, with a massive accumulation of outer segment debris separating the retina from the pigment epithelium and interfering with the close anatomical relationship which should exist between these 2 layers. In spite of the severe

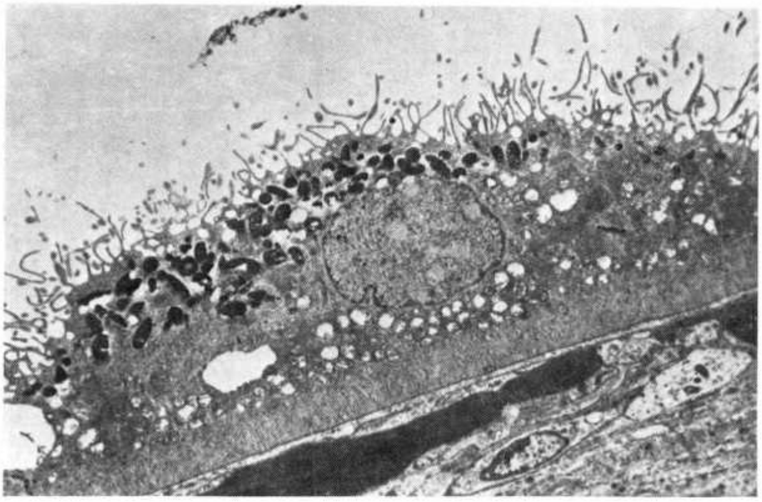
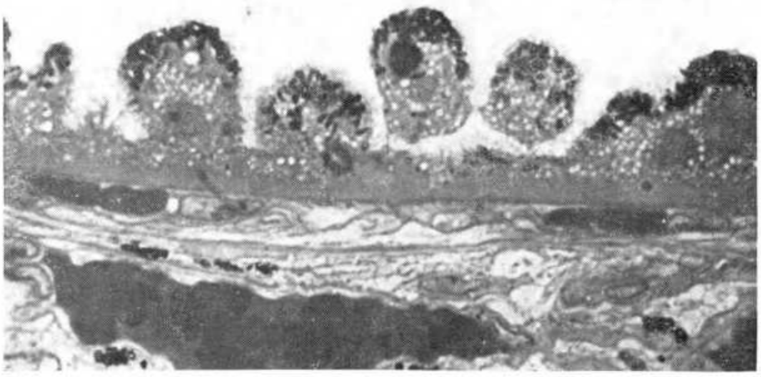


Fig. 5 *Rabbit pigment epithelium in experimental retinal detachment to show absence of phagosomes*

Fig. 6 *Production of mobile macrophage-like cells from rabbit pigment epithelium after experimental detachment of the retina*



disorganisation of the outer retina which follows choroidal ischaemia, a return of blood supply may be followed by a remarkable restoration of near normal structure and a recovery of function as indicated by the reappearance of the previously extinguished electroretinogram (Foulds and Johnson, 1974; Johnson, 1976). This recovery from an ischaemic episode is accompanied by a remarkable increase in phagosomes present in the pigment epithelial cells (Johnson, 1975a) (Fig. 4). This activity appears to be important in the restitution of the normal interface and a return of visual function. In contrast, in established retinal detachment, where after a short time no outer segments survive, the number of phagosomes in the pigment epithelium is reduced to zero (Kroll and Machemer, 1968; Johnson and Foulds, 1977) (Fig. 5).

Macrophage-like cells

In situations where excessively large amounts of outer segment debris overwhelm the phagocytic activity of the pigment epithelium, or where the retina is separated from the pigment epithelium, the epithelium draws upon its pluripotential capacity and appears capable of elaborating mobile cells with many of the characteristics of macrophages. Such cells are seen in the subretinal space in acute ischaemic damage to the retina and very strikingly, in retinal detachment, where their apparent origin from the retinal pigment epithelium can be surmised on morphological grounds (Johnson and Foulds, 1977) (Fig. 6). Although the retinal pigment epithelium appears capable of transforming into macrophage-like cells, many of the macrophages

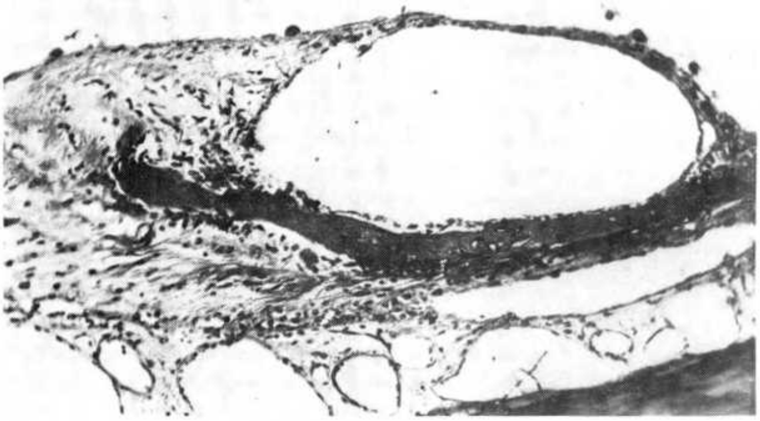


Fig. 7 *Metaplasia of the pigment epithelium with bone formation in rabbit experimental retinal detachment*

found in the subretinal space in, for example, retinal detachment may nevertheless be derived from the blood stream, for Bruch's membrane appears to be no barrier to the passage of cells inwards from the choroid.

Pigmented macrophage-like cells of possible pigment epithelial origin may be seen in a wide variety of pathological processes affecting the interface between the retina and the pigment epithelium, a striking example being retinitis pigmentosa. One possible stimulus to cellular activity in the pigment epithelium is loss of contact inhibition by the retina, either because of physical separation in retinal detachment or by the loss of some inhibitory function which is peculiar to normal outer retina and normal receptors.

In retaining an embryological capacity for multiplication the pigment epithelium seems capable of returning to a more primitive multicellular format and can show a surprising ability as an epithelial layer of neuroectodermal origin to form cells capable of laying down collagen and even bone, a metaplasia which may be strikingly seen when the retinal pigment epithelial interface is broken by retinal detachment (Foulds and Ikeda, 1966) (Fig. 7).

Thus physically breaking the retinal-pigment epithelial interface leads to dramatic changes in structure and function of the pigment epithelium, which may increase its phagocytic acitvity by normal cellular activity or undergo metaplasia to produce actively phagocytic macrophages. Alternatively or additionally, the epithelium may proliferate to form a multilaminar layer, which may take on the characteristics of connective tissue, with the formation of fibrous tissue or even bone, and a loss of the more specialised features of the pigment epithelium.

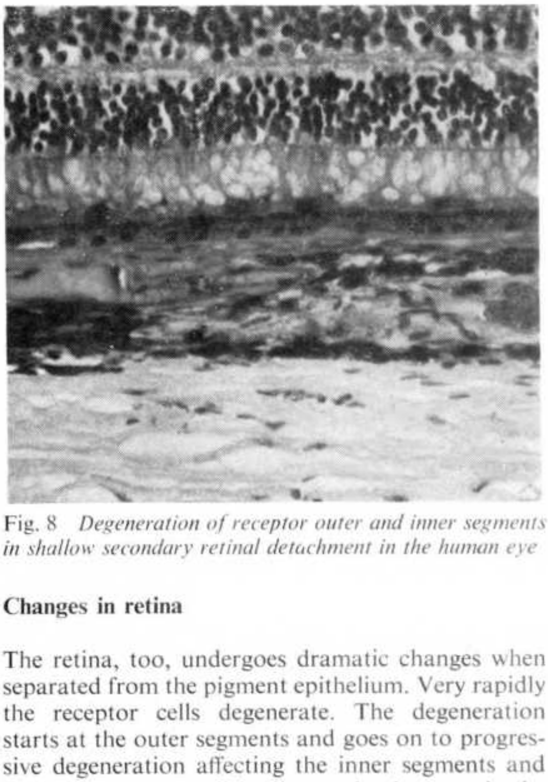


Fig. 8 *Degeneration of receptor outer and inner segments in shallow secondary retinal detachment in the human eye*

Changes in retina

The retina, too, undergoes dramatic changes when separated from the pigment epithelium. Very rapidly the receptor cells degenerate. The degeneration starts at the outer segments and goes on to progressive degeneration affecting the inner segments and then the receptor cell bodies and subsequently the other neural layers from without inwards, until eventually the neural tissue of the retina is replaced by a layer of glial supporting tissue without any visual function whatsoever (Foulds, 1964; Foulds and Ikeda, 1966; Kroll and Machemer, 1968). This degeneration occurs even if the detachment is shallow and appears to be a direct consequence of the separation of the retina from the pigment epithelium (Fig. 8).

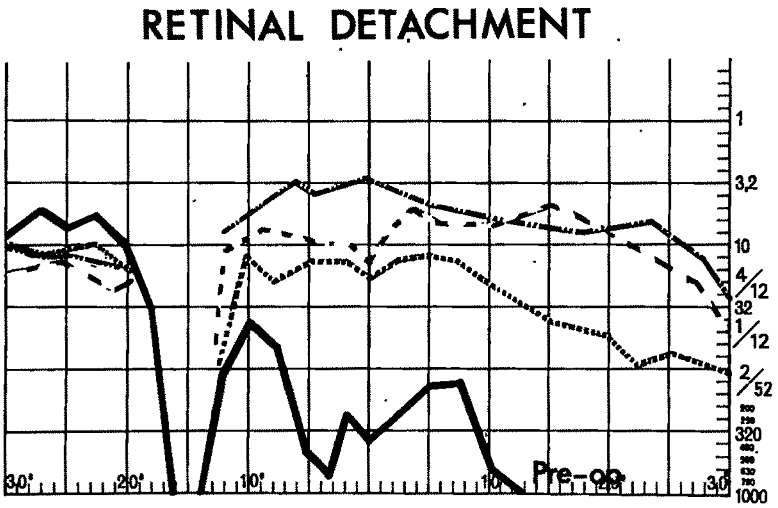


Fig. 9 *Serial static perimetry in a patient treated for retinal detachment. There is progressive increase in retinal sensitivity over a 4-month period, but peripheral retinal function recovers more rapidly than central*

If the retinal-pigment epithelial interface is restored before the receptor cell bodies have degenerated, then regeneration of the inner and outer segments of the receptor cells occurs with a return to a normal anatomical appearance and a recovery of visual function (Foulds, 1964; Kroll and Machemer, 1968). Receptor cell regeneration may well explain the recovery of retinal function which follows surgical cure of a retinal detachment in man. This improvement in retinal function may be reflected by a decrease in the visual field defect, and particularly well by measurements of differential threshold, which may be plotted by static perimetry (Foulds *et al.*, 1974; Chisholm *et al.*, 1975). As can be seen from serial static perimetric profiles, rod vision appears to recover more rapidly than cone vision (Fig. 9).

Measurement of colour vision too is a useful criterion of visual function, and it is of interest that not only is there a rapid improvement in colour vision after successful retinal detachment surgery, but an improvement continuing for a year and sometimes longer is commonly seen (Chisholm *et al.*, 1975). When one looks at the average rate of improvement in colour vision after successful surgery for retinal detachment affecting the macula, one sees a curve which may give an indication of the rate of cone regeneration with a half life of about 12 weeks (Fig. 10).

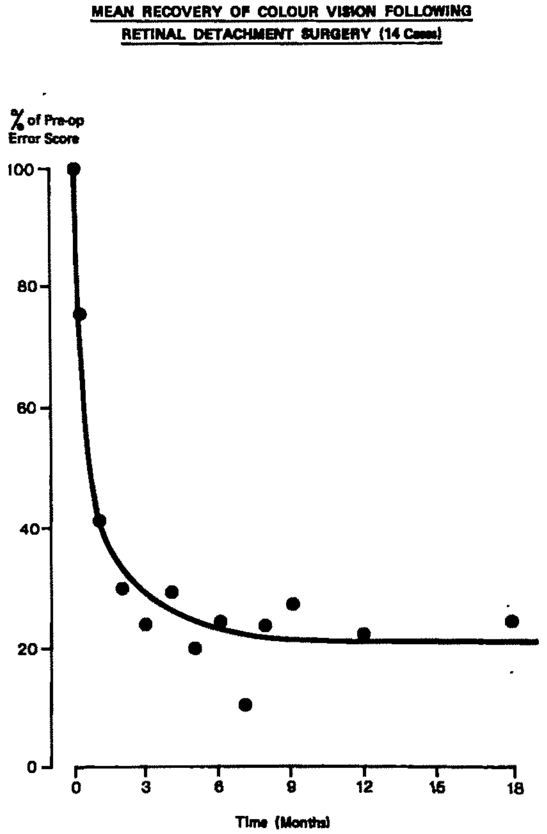


Fig. 10 *Mean rate of recovery of colour vision after successful retinal detachment surgery in 14 cases in which the macula was affected. There is rapid recovery during the first 3 months and slower recovery subsequently*

Electrophysiological findings

Apart from obvious morphological changes which occur in the outer retina and the pigment epithelium when the interface between them has been broken, characteristic changes also occur in electro-physio-

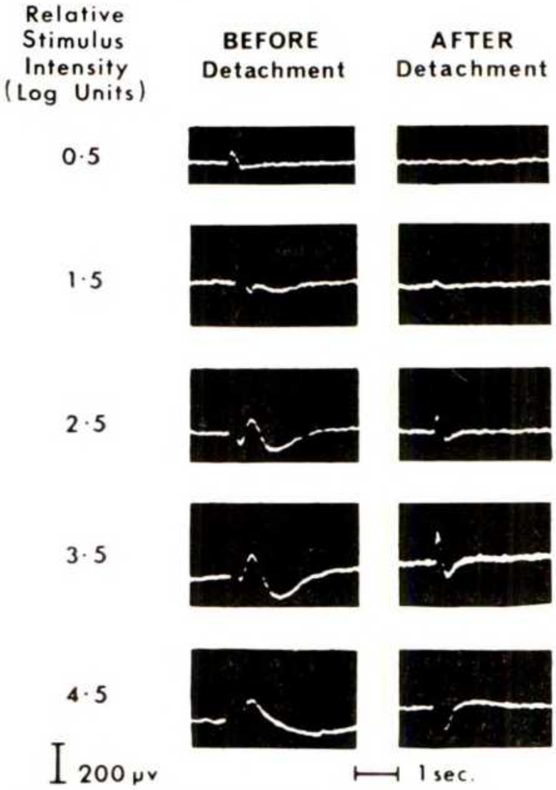


Fig. 11 *Rabbit electroretinograms before and after induction of total experimental retinal detachment. Detachment of the retina results in a reduction in b-wave amplitude and a total abolition of the c-wave*

logical parameters. It is well known that a prolonged separation of the retina from the pigment epithelium is accompanied by abolition of all the components of the electroretinogram (Karpe, 1948) and by an abolition of light-induced changes in the electro-oculogram (Foulds and Ikeda, 1966). One might be tempted to think that all of the electrophysiological alterations are a reflection of the obvious degenerative changes which occur after separation of the retina and the pigment epithelium, but there is evidence that separation of these layers alone is responsible for some of the electrophysological findings. In the rabbit, for example, the scotopic electroretinogram (ERG) shows not only a well developed a- and b-wave but also a c-wave which is thought to represent metabolic activity in the pigment epithelium (Noell, 1953). Separation of the retina from the pigment epithelium causes a decline in the amplitude of the ERG and its eventual abolition over the course of 48 hours or so (Foulds and Ikeda, 1966). If, however, one examines the ERG immediately before and immediately after a total retinal detachment has been induced, one finds that apart from a reduction in the amplitude of the a- and b-waves there is an immediate and total abolition of the c-wave (Fig. 11). The pigment epithelium at this stage looks normal and retains its normal relationship to its blood supply, while the retina too appears structurally intact.

The changes in the ERG therefore suggest that, although the pigment epithelium may be the seat of the c-wave, contact between the retina and pigment epithelium is necessary for its production. Support for this suggestion comes from a study of the standing potential of the eye undergoing acute total retinal detachment (using a modification of the technique described by the author in 1963). Before the retinal detachment has been induced, the standing potential decreases in the dark and increases in the light as expected. Immediately after detachment light-induced changes in the standing potential are abolished, no decrease occurring in the dark and no increase in the light (Fig. 12). When, however, sodium azide is injected intravenously, there is an immediate temporary increase in the corneofundal potential. Sodium azide is known to affect ionic flux across the pigment epithelial cell membranes, and the induced rise in corneofundal potential following intravenous sodium azide is an indication that the pigment epithelium is still functionally active, and once again evidence that the abolition of the electro-oculogram in retinal detachment is not in the first place due to degenerative changes in either the retina or the pigment epithelium, but the direct result of separation of these 2 layers.

It is of interest that if the retinal separation is subtotal the c-wave remains normal, although the b-wave of the ERG is reduced in amplitude commensurate with the area of detachment (Fig. 13). It appears that the whole retinal pigment epithelium can be stimulated to metabolic activity via a localised residual area of retinal pigment epithelial contact, and there are grounds for believing that the pigment epithelial layer acts as a single unit in this respect and not as a series of individual cells. It has been suggested that the electrical continuity of the pigment epithelial layer is established via the gap junctions between neighbouring cells, which allow ionic transfer from one cell to its neighbours (Revel *et al.*, 1972). These junctions are different from the tight junctions near the apices of the cells, which form a diffusion barrier between the choroid and the subretinal space.

Pigmentary degeneration of retina

Many of the features of retinal detachment and indeed of choroidal ischaemia resemble the patho-

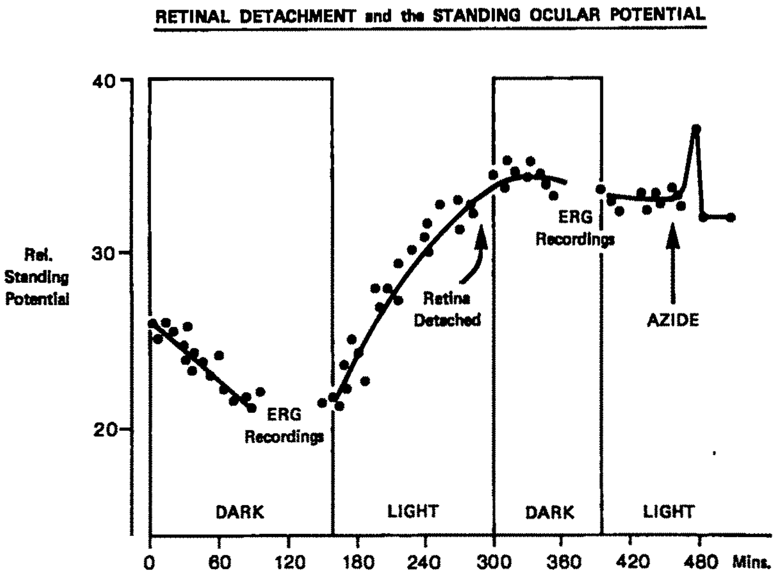


Fig. 12 *Electro-oculogram in rabbit before and after induction of total experimental retinal detachment. Light-induced changes in standing potential are abolished immediately the retina is detached, although azide responsiveness of the pigment epithelium is retained*

logical changes seen in primary pigmentary degeneration of the retina. Indeed atrophy and proliferation of the retinal pigment epithelium, loss of the receptor cell outer segments, and subsequently loss of the inner segments and cell bodies, all of which are features of retinitis pigmentosa, are also features of any pathological process damaging either the outer retina or the pigment epithelium. And it would seem that the clinical picture of retinitis pigmentosa is common to any process which causes damage to the tissues constituting the retinal-pigment epithelial interface.

If primary pigmentary degeneration of the retina is the result of an interference with the close metabolic interrelationships which exist between the pigment epithelial cell and the outer retina, it is interesting to speculate which of the many metabolic activities may be at fault. Certainly one could imagine that in retinal detachment, or in damage to this area from total choroidal ischaemia, any or all of the metabolic functions of the pigment epithelium in relation to the retinal receptors could be affected. In other instances, however, the defect could be more specific.

It is well known, for example, that vitamin A deficiency can in some instances result in a somewhat similar picture to primary pigmentary degeneration, and the work of Dowling and Gibbons (1961) on the effects of vitamin A deficiency in the rat is a classic demonstration of how vitamin A deficiency can produce a reversible degeneration in the outer retina with many features common to the early stages of primary pigmentary degeneration seen in some experimental models.

Classically, in man, vitamin A deficiency is said to show itself first as a loss of rod function with deficient dark adaptation and reduction in peripheral visual field, together with xerotic changes in the superficial ocular tissues. In our experience acquired vitamin A deficiency in the adult, which we see in patients suffering from chronic liver disease, is commonly associated not only with a disturbance in rod function but with a well marked defect of cone function as shown by a reversible loss of visual acuity and by an acquired and reversible dyschromatopsia, together with a reduction in the amplitude of both the scotopic and photopic ERG (Bronte-Stewart and Foulds, 1972).

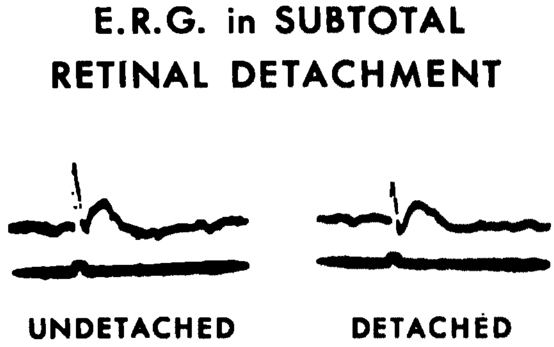


Fig. 13 *Rabbit electroretinogram in subtotal retinal detachment. The amplitude of the b-wave is reduced, but the c-wave amplitude remains normal*

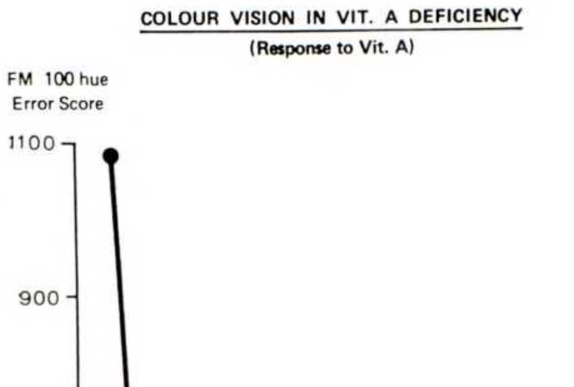


Fig. 14 *Rate of recovery of colour vision in a patient with acquired dyschromatopsia associated with vitamin A deficiency. The rate of recovery is not dissimilar to that following successful treatment for retinal detachment*

The effects of vitamin A deficiency on visual function appear to be inversely related to the degree of illumination to which the retina has been subjected. It is interesting that one of our patients with vitamin A deficiency, finding that she was unable to see as she would like, progressively increased the strength of the electric light bulbs in her house until she had the largest obtainable wattage lamps in every possible socket in the house. The more she increased the illumination, the more rapidly her vision deteriorated. Not only was her visual acuity poor, as might have been expected in someone showing marked vitamin A deficiency, dark adaptation was grossly abnormal. Colour vision too was also extremely defective. Within a week of beginning vitamin A therapy visual acuity and dark adaptation returned to near normal and colour vision improved progressively. Interestingly, the rate of improvement of colour vision on vitamin A therapy paralleled that seen after retinal detachment surgery (Fig. 14), a relationship suggesting a similar process of cone recovery or regeneration with a half life of about 12 weeks. When this patient's vision improved she found the previous level of illumination at home distressingly painful to her now normal vision and rapidly reduced the strength of the electric light bulbs to a more conventional level.

This effect of light is of course to be expected, the rate of breakdown of visual pigment being related directly to the amount of light being absorbed, and it is easy to imagine that if regeneration of visual pigment is defective for any reason photic stress is likely to exaggerate the defect. Thus in the RCS rat, for example, which develops a primary pigmentary degeneration of the retina, the process is delayed if the animals are reared in the dark (Herron *et al.*, 1969), which suggests that in these animals pigmentary degeneration is related to the process of bleaching and resynthesis of visual pigment.

There are in man conditions in which vitamin A deficiency is associated with a pigmentary degeneration of the retina. Thus, in the rather rare condition of abetalipoproteinaemia one finds an inability to absorb the fat soluble vitamins and low levels of vitamin A and of carotenes in the serum. In 2 patients we have investigated recently vitamin A and carotene levels were extremely low, and both patients showed the characteristic pigmentary retinopathy which has been described in the Bassen-Kornzweig syndrome (Bassen and Kornzweig, 1950), with marked choroidal 'show-through' on fluorescein angiography (Fig. 15). There was a widespread reduction in retinal sensitivity affecting both the peripheral retina and the central retina, with gross visual field defects and an acquired achromatopsia. Dark adaptation was abnormal and the photopic and scotopic electroretinograms were unrecordable. In 1 case treatment with large doses of intramuscular vitamin A resulted in a rapid return to normal of dark adaptation (Fig. 16) and of the electroretinogram (Fig. 17). There was slight improvement in central vision but a marked improvement in visual field (Fig. 18). Interestingly, the retinol binding protein level, which initially was undetectably low, returned to normal on treatment with vitamin A. This suggests that the amount of retinol binding protein in the blood was a reflection of the amount of vitamin A to be transported and

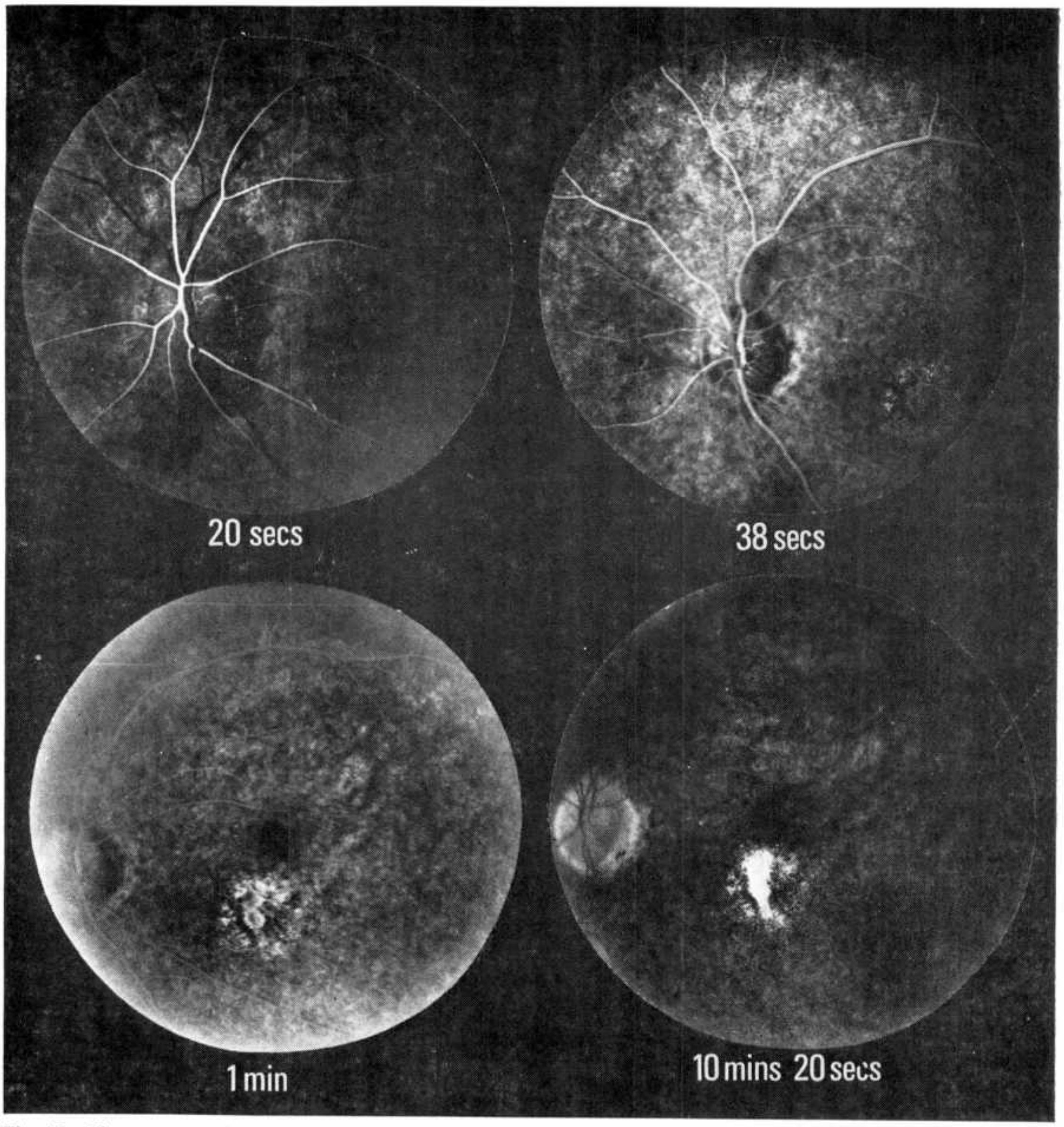


Fig. 15 *Fluorescein angiograms in a patient suffering from abetalipoproteinaemia. There is marked abnormality of the pigment epithelium with choroidal 'show-through' and late staining of a gliotic area below the macula*

that in these patients the reported depression of retinol binding protein levels may be secondary to the vitamin A deficiency.

The response of dark adaptation and of peripheral field to vitamin A in one of these patients was gratifying but the lack of recovery of central vision disappointing. Recently we have measured this patient's essential fatty acid levels and have found these to be extremely depressed. There is evidence that outer segment turnover is dependent on polyunsaturated fats (Anderson *et al.*, 1974), and it may be that the receptor abnormality in patients with the Bassen-Kornzweig syndrome is multifactorial, vitamin A and essential fatty acids being two of the factors involved. Indeed our findings of poor colour vision in vitamin A-deficient patients suffering

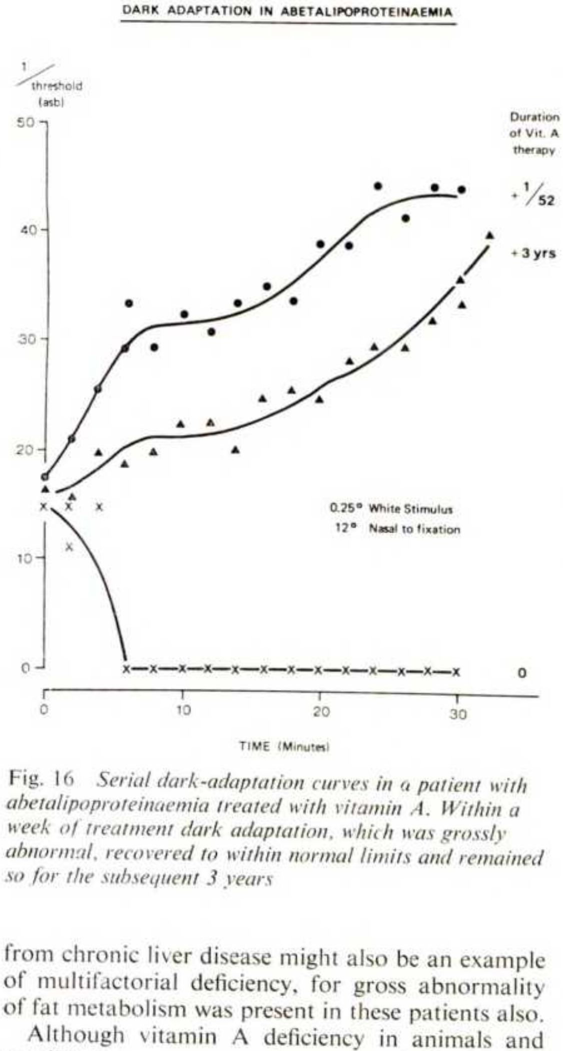


Fig. 16 *Serial dark-adaptation curves in a patient with abetalipoproteinaemia treated with vitamin A. Within a week of treatment dark adaptation, which was grossly abnormal, recovered to within normal limits and remained so for the subsequent 3 years*

from chronic liver disease might also be an example of multifactorial deficiency, for gross abnormality of fat metabolism was present in these patients also.

Although vitamin A deficiency in animals and possibly in man can produce some of the features of retinitis pigmentosa, there is little doubt that human retinitis pigmentosa is not due to overt vitamin A deficiency, for it is well known that no support for this simplified concept is to be found in examination of vitamin A metabolism in patients suffering from this condition. Nor does it seem likely that an abnormality in the retinol binding protein, which transports vitamin A from the liver to the eye, is a consistent finding in patients with retinitis pigmentosa (Rahi, 1972).

Passage of metabolites

In relation to retinol binding protein a slight digression may be in order. When one looks at the basal region of the pigment epithelial cell one finds that the basal lamina is remarkably convoluted, so that its surface area is greatly increased, a modification no doubt designed to increase the ease of transfer of metabolites between pigment epithelial cells and the underlying choriocapillaris. The choriocapillaris too is oddly specialised, in that, unlike the majority of capillaries in the body, it is fenestrated, with obvious breaks in the capillary basement membrane, the individual fenestrations being directed towards the pigment epithelium (Porter and Yamada, 1960; Bernstein, 1961; Leeson and Leeson, 1968).

Why should these capillaries be so fenestrated? One might argue that the breaks will facilitate the passage of metabolites from the lumen of the choriocapillaris to the extravascular space, but in other situations, such as in the retina and the brain, the high metabolic requirements of the tissues are met without this modification. An alternative explanation would be the need to allow the passage outwards from the choriocapillaris of larger molecules than could escape by diffusion through the intact vessel wall. It is known that retinol binding

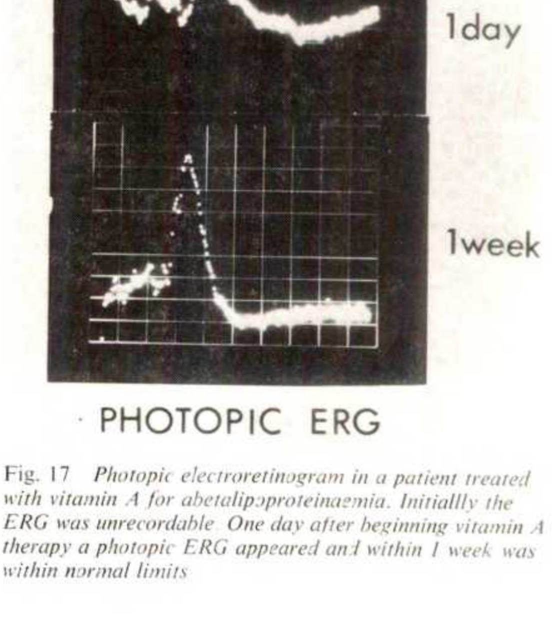


Fig. 17 *Photopic electroretinogram in a patient treated with vitamin A for abetalipoproteinaemia. Initiallly the ERG was unrecordable. One day after beginning vitamin A therapy a photopic ERG appeared and within 1 week was within normal limits*

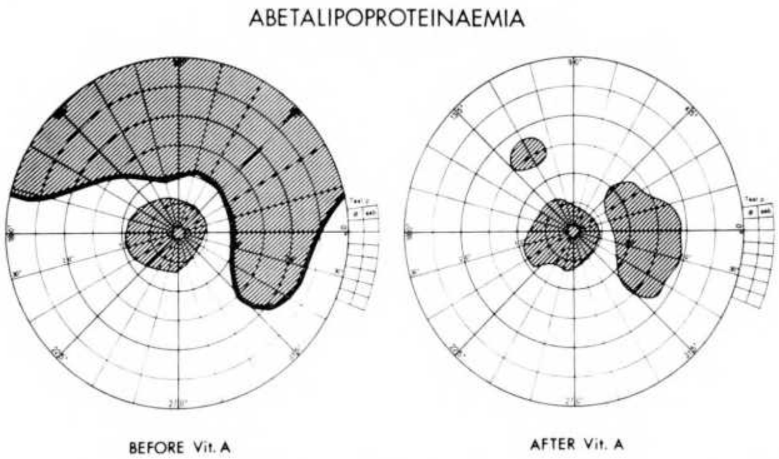


Fig. 18 *Recovery of visual field in a patient treated for abetalipoproteinaemia with vitamin A. Improvement in field occurred over a period of about 4 weeks*

protein has a molecular weight of about 21 000, and it is also known that there are specific binding sites on the basal aspect of the pigment epithelial cell for retinol binding protein (Young and Bok, 1970; Heller, 1975; Bok and Heller, 1976). It would seem reasonable that the fenestrations are there to allow retinol binding protein with its vital retinol access to the pigment epithelial cell from the choroid.

As a corollary this would allow the leakage of other large molecules, such as the plasma proteins, and, as the presence of proteins within the eye decreases light transmission, it would be necessary to restrict the forward diffusion of these proteins, a circumstance achieved by the provision of zonulae occludentes between neighbouring pigment epithelial cells. It is interesting that these junctions are apical, so that the whole of the pigment epithelial cell, apart from its apical surface, is bathed in proteinous fluid and therefore exposed to retinol binding protein. As a further corollary, the eye has the problem of how to dispose of plasma protein which has leaked from the choriocapillaris. In general extravascular protein is returned to the circulation via the lymphatic system, but no lymphatics exist in the eye. The nearest lymphatics are in the orbit, and there is evidence for the existence of a transscleral movement of even large molecules under the influence of the intraocular pressure, an arrangement which may be designed to allow access to the orbital lymphatics of choroidal protein which has of necessity become extravascular (Foulds, 1976).

The utilisation of vitamin A in the synthesis and resynthesis of visual pigment involves a complicated series of biochemical events, which includes not only absorption of vitamin A from the gut and its storage in the liver but its transport by retinol binding protein to the eye and its subsequent binding on specific receptor sites on the pigment epithelial cell wall. It is known that a variety of transferases are involved in transferring the retinol into the pigment epithelial cell, out of the retinal pigment epithelial cell and into the inner segment of the retinal receptor cell (Dowling, 1960; Young and Bok, 1970).

In both the pigment epithelial cell and the inner segment of the retinal receptor cell there are separate retinol binding proteins of different molecular weights to plasma retinol binding protein, and in addition there are probably enzymic reactions involved in the conjugation with opsin and the production of the membranes which form the basis of the stacked discs in the outer segment. Enzymic reactions are undoubtedly involved in the phagocytosis and metabolism of outer segment material by the pigment epithelial cell and also in the reversible changes which occur during the normal processes of bleaching and regeneration of the visual pigment associated with the initiation of the visual impulse.

It seems at least possible that a failure of any of these steps, many of which involve specific enzymic activity, could lead to a breakdown in the synthetic pathways of visual pigment or in the turnover of outer segment material and result eventually in the structural changes which may underly the development of retinitis pigmentosa. If this is true, then any one of perhaps 20 or 30 steps could be involved, and the possibility exists that there may be as many as 20 or 30 different types of retinitis pigmentosa. Apart from vitamin A the role of other metabolites has to be considered, and these include fatty acids and amino acids such as taurine.

Conclusion

If the group of diseases which present with pigmentary degeneration of the retina are considered to share a final common mechanism, that would allow us to include not only vitamin A deficiency but rarities like abetalipoproteinaemia in the same category and such diverse conditions as retinal detachment, choroidal ischaemia, and even light damage to the retina. Thus, the mechanisms underlying a wide variety of pigmentary disturbances in the fundus can be thought of as pigment epithelial-retinal interface diseases, and a condition such as retinitis pigmentosa, which clinicians tend to regard as an entity, may represent a whole group of as yet inadequately described and ill understood genetically determined biochemical abnormalities.

The interface between the retina and the pigment epithelium is basic to the visual process, and a better understanding of the interrelationships between these 2 cell layers may both add to our concepts of normal physiology and improve our understanding and management of the many pigmentary retinopathies which at present remain a mystery to the ophthalmologist and a tragic misfortune to those affected.

I should like to record my gratitude to the various members of the Tennent Institute of Ophthalmology in Glasgow, whose material has formed the basis of this lecture, and in particular to Dr W. R. Lee, ophthalmic pathologist, for his constant help, and to Drs Johnson and Grierson for permission to reproduce some of their electronmicrographs. I thank Dr Shaw Dunn, of the Department of Anatomy, Glasgow University, for the embryological preparations, and I particularly thank Dr Hisako Ikeda, of St. Thomas's Hospital Medical School, who many years ago worked with me on the functional and structural effects of retinal detachment and some of whose joint work is presented here. I am particularly grateful to her as she was largely responsible for kindling my interest in the retinal-pigment epithelial interface.

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Senile disciform macular degeneration: features indicating suitability for photocoagulation

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SUMMARY During a 1-year period 398 new patients were seen with disciform macular degeneration (530 eyes). The lesions were studied retrospectively, and those in which the neovascular tissue did not underlie the fovea, and therefore were treatable, were identified. The following conclusions were drawn: (1) Treatment is possible in most patients with good acuity and few with poor acuity. (2) Treatment is possible in a large proportion of patients with a short history and few with a long history of visual loss. (3) As many as 50% of all patients with senile disciform macular degeneration may be amenable to treatment if seen early enough in the course of their disease. (4) Over one-third of eyes with lesions that are untreated have a visual acuity of 6/60 or better 3 years after the onset of symptoms. (5) If a controlled trial proves that treatment is beneficial, these results emphasise the need for rapid referral and show that these patients will generate a large additional clinical load.

The early reports of photocoagulation in senile disciform macular degeneration showed poor visual results after treatment (Zweng *et al.*, 1968; Schneider, 1970; l'Esperance, 1971). With a better understanding of the disease process (Gass, 1967; Teeters and Bird, 1973a,b) a more rational approach to photocoagulation has evolved. This, coupled with the introduction of argon laser photocoagulation and its adaptation to the slit lamp (l'Esperance, 1968; Little *et al.*, 1970) has given rise to better visual results (Schatz and Patz, 1973; Gass, 1973; Bird, 1974; Bonnet, 1975; Hirose, 1976; Sand, 1977). The most recent experiences suggest that photocoagulation for disciform macular disease may be justifiable and certainly indicate the need for a randomised clinical trial to test its true value.

A variety of factors have been identified during feasibility studies which suggest that the value of photocoagulation may be limited. Photocoagulation does nothing to alter the basic disease process, so that recurrences can be expected (Bird, 1975). Secondly, it has become evident that only a minority of disciform lesions are amenable to therapy when first seen because the neovascular tissue underlies the fovea in most patients.

This retrospective study was undertaken to determine the percentage of disciform lesions referred to the Retinal Diagnostic Department at this hospital which were amenable to photocoagulation and to identify those clinical attributes which may guide the clinician as to the likelihood of the lesion being suitable for photocoagulation. This information may give some indication about the management of disciform macular disease, and what the size of the clinical load might be if clinical trial shows this form of treatment to be justifiable.

Materials and methods

Fluorescein angiograms of all new non-diabetic patients referred to the Retinal Diagnostic Department of Moorfields Eye Hospital were examined retrospectively for the 12-month period from 1 December 1976 to 5 December 1977. Those angiograms which were found to have neovascular disciform lesions or pigment epithelial detachments were further subdivided according to the supposed aetiology of the disease.

Senile disciform degeneration was diagnosed in those patients over 50 years of age with drusen and pigment epithelial changes in addition to subretinal neovascularisation and in whom there was no evidence of other cause for their disease. The visual acuity and the duration of symptoms at the time of angiography were recorded for each affected eye.

Treatment by argon laser photocoagulation was considered possible in those eyes in which the sub-

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retinal neovascular membrane could be clearly defined and in which there was a discernible gap between the edge of the neovascular tissue and the foveola (about 100 μm). The possibility of argon laser treatment at the time of angiography was related to the visual acuity and the duration of symptoms in affected eyes.

Patients in the older age group with pigment epithelial detachments associated with drusen were also identified, since these may precede the onset of vascular disciform lesions (Gass, 1967; Teeters and Bird, 1973b). All such lesions were considered potentially treatable.

All those patients who had had disciform degeneration for 3 years or more before angiography were analysed in order to identify the prognosis for visual acuity in untreated eyes.

Results

Two thousand non-diabetic patients were seen during the 12-month period of the study, and 530 eyes (398 patients) had subretinal neovascularisation (Table 1); 20% of all senile disciform lesions were potentially treatable at the time they were first seen; this compares with 32% in the younger group.

Table 2 shows the visual acuities of the patients with senile subretinal neovascular lesions at the time of fluorescein angiography. Argon laser treatment was theoretically possible in 90% of cases with an acuity of 6/12 or better. Conversely, the lesions were found to be untreatable in over 98% of cases with vision as low as 6/60, and no treatable cases were found once the vision had deteriorated to below 6/60. Fig. 1 shows the reduction of the number of treatable disciform lesions with the drop in visual acuity. Well over half the eyes (255 of 443; 58%) when first seen fell into the group with an acuity of 6/60 or worse, and therefore there was little chance of their being suitable for treatment.

Table 1 *Number of eyes with treatable and untreatable subretinal neovascularisation and pigment epithelial detachments*

	Treatable	*Untreatable*	*Pigment epithelial detachment*	*Total*
Senile	90	355	63	508
POHS*	9	11	0	20
Myopia	4	24	0	28
Others	14	23	3	40
Total	117	413	66	596

* Presumed ocular histoplasmosis syndrome.

The length of time the patients were symptomatic before fluorescein angiography was found to be related to the number of treatable senile disciform lesions (Table 3, Fig. 2); 83% of lesions were treatable when symptoms had been present for 2 weeks or less. This percentage fell to 43% at 1 month and to 30% at 4 months. When symptoms had been

Table 2 *Number of treatable senile neovascular disciform lesions related to visual acuity at angiography (1 treatable and 1 untreatable eye had no acuity recorded)*

Acuity	*Treatable*		*Untreatable*		*Total*
	No.	*(%)*	*No.*	*(%)*	
6/6	3	(100)	0	(0)	3
6/9	16	(84)	3	(16)	19
6/12	15	(94)	1	(6)	16
6/18	32	(48)	34	(52)	66
6/24	11	(31)	24	(69)	35
6/36	9	(20)	37	(80)	46
6/60	3	(4)	67	(96)	70
<6/60	0	(0)	188	(100)	188
Total	89	(20)	354	(80)	443

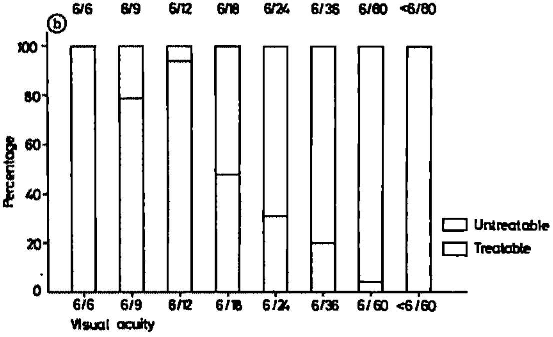

Fig. 1 (a) *Number of treatable and untreatable patients related to visual acuity at angiography*. (b) *Percentage of treatable patients of each acuity*

Table 3 *Number of treatable senile neovascular disciform lesions related to duration of symptoms (3 treatable and 18 untreatable eyes had no exact duration recorded)*

Duration of symptoms	*Treatable*		*Untreatable*		*Total*
	No.	(%)	*No.*	(%)	
0–2 weeks	10	(83)	2	(17)	12
3–4 weeks	15	(43)	20	(57)	35
5–8 weeks	11	(35)	20	(65)	31
9–12 weeks	21	(47)	24	(53)	45
3–4 months	6	(30)	14	(70)	20
5–6 months	5	(10)	47	(90)	52
7–8 months	2	(12)	14	(88)	16
8–12 months	7	(11)	57	(89)	64
Over 12 months	1	(1)	125	(99)	126
Asymptomatic	9	(69)	4	(31)	13
Total	87	(21)	327	(79)	414

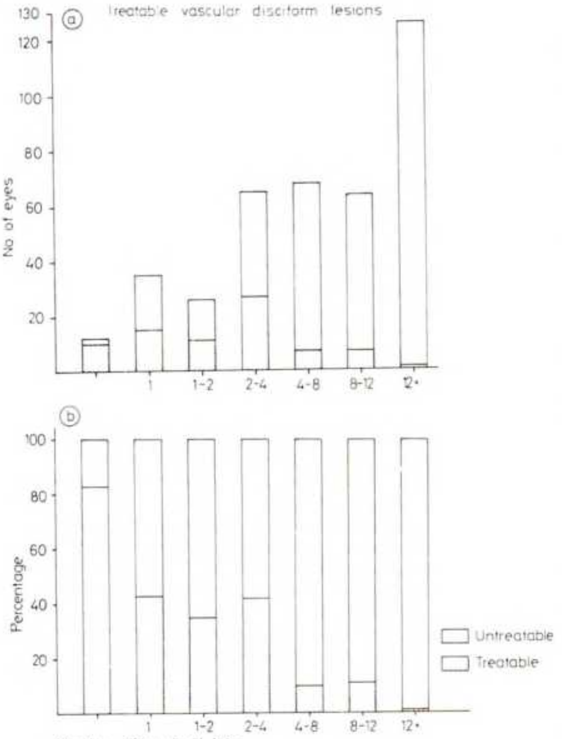

Fig. 2 (a) *Number of treatable and untreatable patients related to duration of symptoms.* (b) *Percentage of treatable patients related to duration of symptoms*

present for over 1 year, only 1% of the eyes had treatable lesions. The group of eyes which could have been predicted as being untreatable because symptoms started more than 4 months previously were a majority of those seen (243 of 414; 59%).

Thirteen patients with senile disciform degeneration in 1 eye had asymptomatic lesions in the fellow eye; 69% of these asymptomatic lesions were treatable.

Pigment epithelial detachments were found in 63 eyes in the group of patients with senile degeneration. These included both subfoveal and parafoveal detachments, and all were considered to be theoretically treatable except those in which the lesion was so small that photocoagulation would have involved the fovea.

Disciform lesions which had been present for 3 years or more had a better prognosis in the younger patients than in the elderly. Ten out of 15 younger patients (67%) had a final acuity of 6/60 or better and 5 (33%) had 6/24 or better. In the older group 24 out of 76 (32%) had 6/60 or better.

Discussion

The proportion of treatable lesions obtained in this series is not necessarily representative of disciform degeneration in the general ophthalmic outpatient population of this hospital owing to prior selection for fluorescein angiography; patients with longstanding disciform changes are less frequently investigated. Thus, in the eyes with senile neovascular changes the treatable number obtained here of 20% (30% including pigment epithelial detachments) may be too high in relation to the total number of patients with senile disciform disease presenting to the hospital clinics. On the other hand some eyes included in the study did not afford the primary reason for the patients' referral to us, since it was the fellow eye of one with recent visual loss. However, analysis of those patients who were considered treatable may offer useful guides to the clinician when trying to assess the likelihood of treatment being possible.

The chance of a disciform lesion being treatable may be predicted from the visual acuity alone. In this study an affected eye with an acuity of 6/24 or better had at least a 1-in-3 chance of having a treatable lesion, but once the acuity had fallen to 6/60 or worse the chances were remote.

More important was the correlation between the proportion of treatable lesions in patients and the length of history of visual loss. 53% seen within 1 month were treatable, whereas the figure was only 15% when the symptoms had lasted over 4 months and 1% when over 1 year. This is not surprising, since progression is to be expected. Subretinal neovascular tissue, which originates eccentrically, has a tendency to expand, with a predilection for growth towards the fovea (Teeters and Bird, 1973b). This explains not only the loss of visual acuity but also the progression to being untreatable with the passage of time. This predictability of progression is important. It might be argued that a lesion in which the neovascular tissue does not underlie the fovea after 4 months is unlikely to progress further and may not need therapy. The fact that only 1 patient with a long history had a treatable lesion would suggest that this is not valid. However, with long-standing untreated lesions the ultimate visual outcome would argue against photocoagulation of subfoveal neovascular tissue. That 32% of older patients and 67% of younger patients retained or regained an acuity of 6/60 or better renders photocoagulation of the fovea difficult to justify.

It is relevant that a relatively large proportion of lesions were suitable for photocoagulation when seen early in their disease. There is no reason to believe that those seen early were different from those seen late, and it is likely that a much larger proportion of the latter group would have been treatable had they been seen earlier. The proportion of treatable lesions is encouraging, and is much higher than we expected. These figures imply that if photocoagulation proves to be an effective form of therapy it could be available to a large number of patients if systems of referral and assessment are speeded up.

The present justifiable demand that new therapeutic agents be assessed by controlled trial before they become accepted into routine medical practice gives rise to new problems in organising the delivery of health care. This is particularly important if the new form of treatment requires expensive equipment and additional staff. The treatment remains experimental before the trial is completed and yet if it is shown to be effective by trial it becomes justifiable and should be universally available. The former practice, which allowed the gradual evolution of new therapy over a period of decades, has been replaced by a situation where a rapid solution is required. The management of diabetic retinopathy recently proved (Diabetic Research Group, 1976; Cheng, 1976) illustrates the difficulties generated by the advent of clinical trials. Therefore, before a trial is completed, information is required on the natural history and population incidence of the disease in order to plan in advance the provision of the new therapy.

Clearly, if controlled trials show that patients with treatable disciform lesions derive benefit from photocoagulation, systems of referral and treatment ought to take account of our observations if they are representative of the disease. A large proportion of lesions are treatable if seen early in the course of the disease, but extension of the subretinal neovascular tissue beneath the foveola will occur in nearly all cases, and photocoagulation of such advanced lesions is unlikely to be justifiable. Once disciform macular disease is identified the patient should be investigated urgently. Delays may occur between the request from the patient to be seen and the first examination by the ophthalmologist, in providing and assessing the fluorescein angiogram, and in initiating therapy. Inordinate delay at any stage may render a treatable condition untreatable. The late arrival of a large proportion of the patients at our clinic attests to the presence of such delays in the system of referral. Education of the patients (and in Britain of general practitioners) would reduce the interval between the onset of symptoms and the first request by the patient for medical help. This could certainly be achieved in the patients who have sought ophthalmic help because 1 eye had already been affected, for in them there is a risk of the second eye being affected of 12% per year (Gregor *et al.*, 1977).

If controlled trial shows photocoagulation to be beneficial the clinical load which may be generated by disciform degeneration and its treatment will depend on its prevalence and the proportion of lesions likely to be treatable. There is no doubt that disciform macular degeneration is common. It has been estimated to account for 35% (Sorsby, 1966) of the blind population in Caucasian societies, and the incidence of visible macular changes in the elderly of such societies is estimated as being 30% (Kornschweig *et al.*, 1957). The figures in this study suggest that photocoagulation may be justifiable in a large proportion of lesions, so that the additional clinical load could be great. Prompt referral and ready availability of treatment facilities will be ncessary to take advantage of this form of therapy.

We thank Mr K. Sehmi for drawing the graphs and Miss Jayne Fisher for typing the manuscript.

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Bilateral symmetry of vision disorders in typical retinitis pigmentosa

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SUMMARY Bilateral symmetry of disorders of vision is examined in 60 typical patients with retinitis pigmentosa. We observed a very high degree of interocular congruence in the patterns of both kinetic visual field defects and threshold profiles and in abnormalities of foveal colour discrimination and visual acuity. Abnormalities of foveal colour vision are highly correlated with the extent of visual field loss.

Typical retinitis pigmentosa (RP) is a clinical syndrome of inherited diffuse pigmentary retinal dystrophy characterised by (1) nyctalopia, (2) mid-peripheral ring-like scotoma or field contraction, (3) narrowed retinal arterioles, (4) mid-peripheral intraretinal 'bone-spicule' pigmentation, (5) relatively good visual acuity until late in the course of the disease, and (6) no known toxic, systemic metabolic, or inflammatory origin of the degeneration. The various modes of inheritance of typical RP have been identified as autosomal dominant, autosomal recessive, X-linked, and sporadic, usually assumed to be recessive in origin (Jay, 1972). It is a general clinical impression that progression of the disease is bilaterally symmetrical (Pearlman, 1977), although exceptions to this symmetry have been epitomised in cases described as 'unilateral retinitis pigmentosa' (Carr and Siegal, 1973).

The documentation of bilateral symmetry has received little formal attention. Gonin (1901), in describing the ring scotoma as a characteristic feature of typical RP, concluded from 6 of his own cases and a review of 20 other cases that the ring scotoma was 'bilateral and symmetric'. Zeavin and Wald (1956) noted a strong bilateral symmetry in absolute threshold profiles measured in 6 RP patients. Biro (1963), briefly summarising observations of fundus pigmentation in over 500 cases, concluded that the 'tendency to symmetrical development (of intraretinal pigmentation) is extremely characteristic'.

The present study examines bilaterial symmetry of vision disorders in 60 typical RP patients. We observed a very high degree of bilateral similarity in the pattern of kinetic visual field defects, absolute threshold profiles, and abnormalities in foveal colour discrimination and visual acuity. Furthermore, the present study finds that the abnormalities of foveal colour vision are highly correlated with the extent of visual field loss.

Patients and methods

We evaluated 60 patients meeting our 6 criteria of typical RP (outlined above). Patients ranged in age from 8 to 70 years. The modes of inheritance were distributed as follows: 33% autosomal dominant, 4% X-linked, and 63% autosomal recessive or sporadic. Informed consent was obtained from each patient participating in the study.

All tests were performed monocularly on each eye of each patient. After correction of refractive error the visual acuity was determined. Kinetic visual fields were measured with a Goldmann perimeter using the V/4 target. Colour discrimination was measured with the Farnsworth-Munsell 100 hue test using a Macbeth illuminant.

Absolute thresholds were measured at the fovea and at 7 to 11 peripheral positions along each of 4 semimeridians (nasal, temporal, superior, and inferior) employing the Tübinger perimeter (Sloan, 1971). Threshold values were obtained for a blue-

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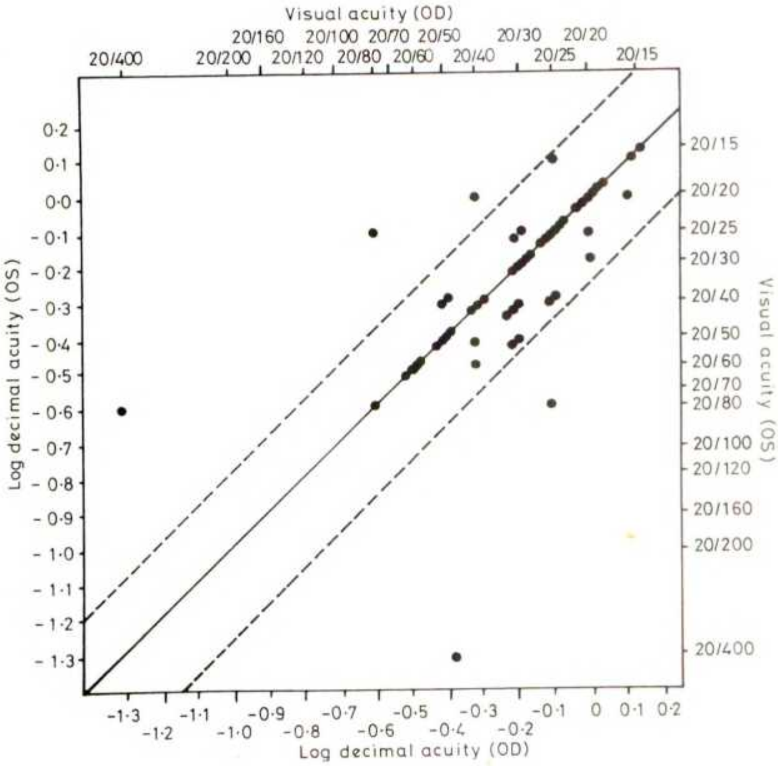

Fig. 1 *Log decimal visual acuity of right eye is plotted against log decimal visual acuity of left eye for each patient (points). Snellen notation is also indicated on the figure. The dotted lines bound a range of ±0·3 log units (approximately ±1 line on the visual acuity chart)*

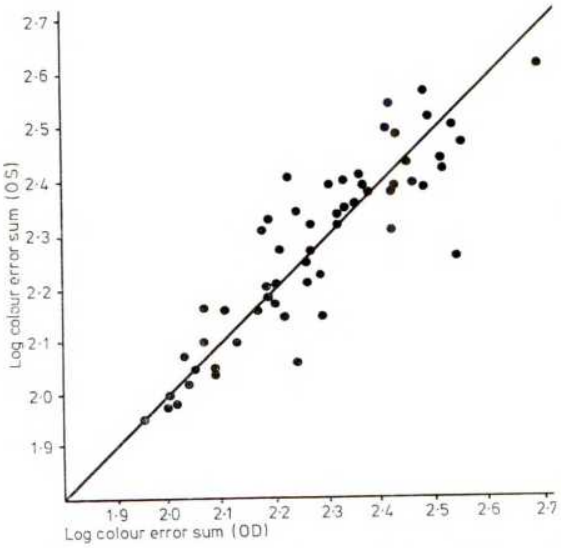

Fig. 2 *Log colour error sum for the right eye is plotted against the log colour error sum for the left eye for each patient (points)*

green light ($\lambda_{max} = 500$ nm), subtending a visual angle of 2°, and flashed on a dark background for 500 milliseconds. The patient was dark-adapted for 45 minutes prior to the threshold measurements. Absolute thresholds were defined as the mean of 3 to 5 repetitions of an ascending method of limits (from below threshold) and were expressed as log relative values (maximum luminance = 2·1 fL).

Results

VISUAL ACUITY

Visual acuity fractions were converted to log decimal acuity.* In Fig. 1 log decimal visual acuity for the right eye is plotted against the log decimal visual acuity for the left eye for each patient. If perfect bilateral symmetry were obtained, all the data points in Fig. 1 would fall on the solid diagonal line, that is, a perfect correlation between the 2 eyes would exist. To determine the extent of correlation between the visual acuities of the right and left eye a product moment correlation coefficient was calculated. A high correlation was obtained (r = 0·63;

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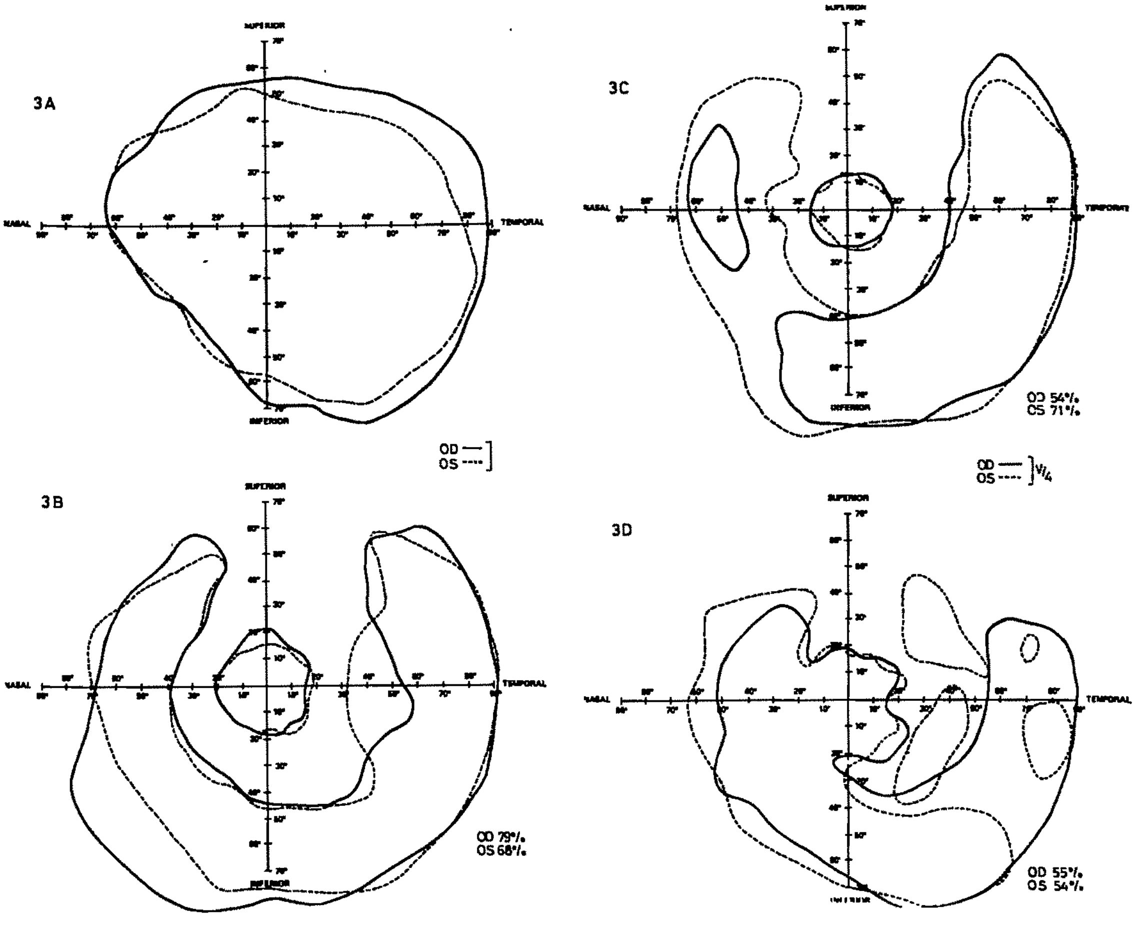
*Each line of the visual acuity chart represents approximately equal changes in angular subtense on a logarithmic scale.



Figs 3a, 3b

Figs 3c, 3d

Fig. 3 *Representative examples of visual fields from (A) a normal observer and (B–J) retinitis pigmentosa patients for the right eye (solid line) and left eye (dashed line), employing the V/4 target on the Goldmann perimeter. Visual fields for both eyes are plotted with respect to nasal and temporal orientation to compare patterns of field loss. The lines bound areas in which the target can be seen. The percentage of normal visual field area is indicated for each pair of fields*

a perfect correlation is r=1·00), indicating that visual acuity in the right eye parallels visual acuity in the left eye.

COLOUR DISCRIMINATION

The results of the Farnsworth-Munsell 100 hue test were converted to a single error score by taking the log of the sum of all errors.† In Fig. 2, the error score for the left eye is plotted against the error score for the right eye. If perfect symmetry were obtained, all the data points would fall on the diagonal line. Calculation of the product moment correlation yielded a very high coefficient (r=0·88), indicating that loss of colour discrimination in the right eye parallels the loss in the left eye.

VISUAL FIELDS

A qualitative assessment of bilaterial symmetry in the pattern of visual field loss was made by plotting the mirror image of the visual field for the left eye over the visual field for the right eye. Fig. 3 illustrates representative examples of these comparisons.

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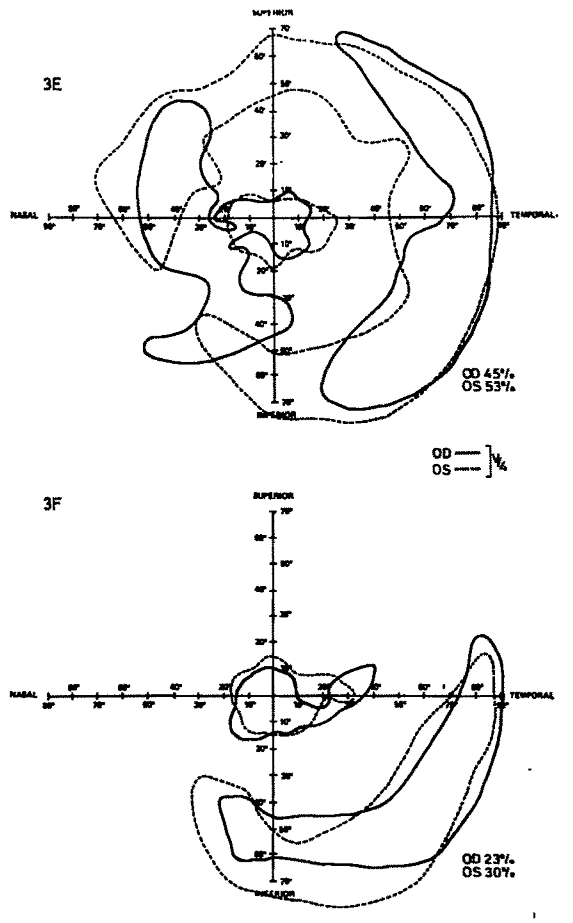
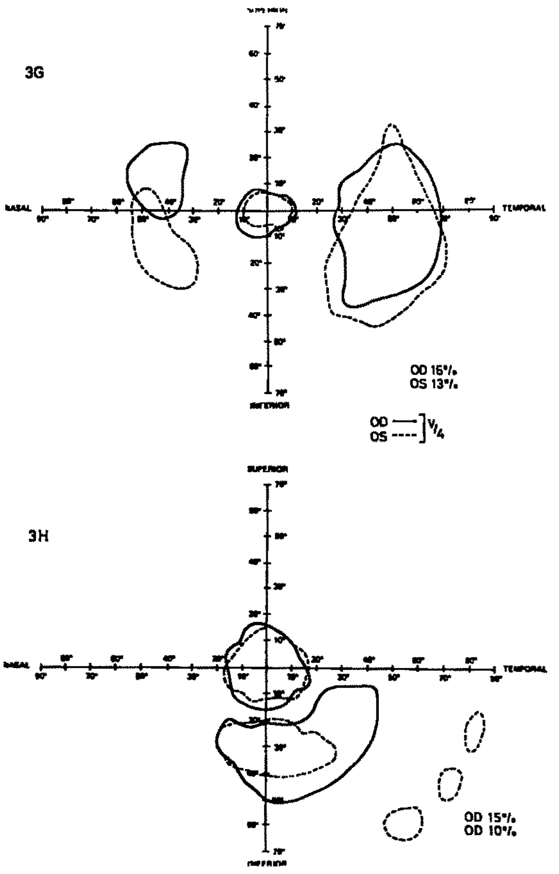
† The log of the error sums is employed because the variability in the error sums is proportional to the mean error sum.



Figs 3e, 3f



Figs 3g, 3h

Each visual field was converted to a single number by measuring the total area of visual function with a planimeter. The resulting visual field area is expressed as a percentage of normal by dividing each value by the area of the average normal visual field. The numbers beside the visual fields in Fig. 3 indicate the measured areas of visual function (expressed as percentage of normal) for each example.

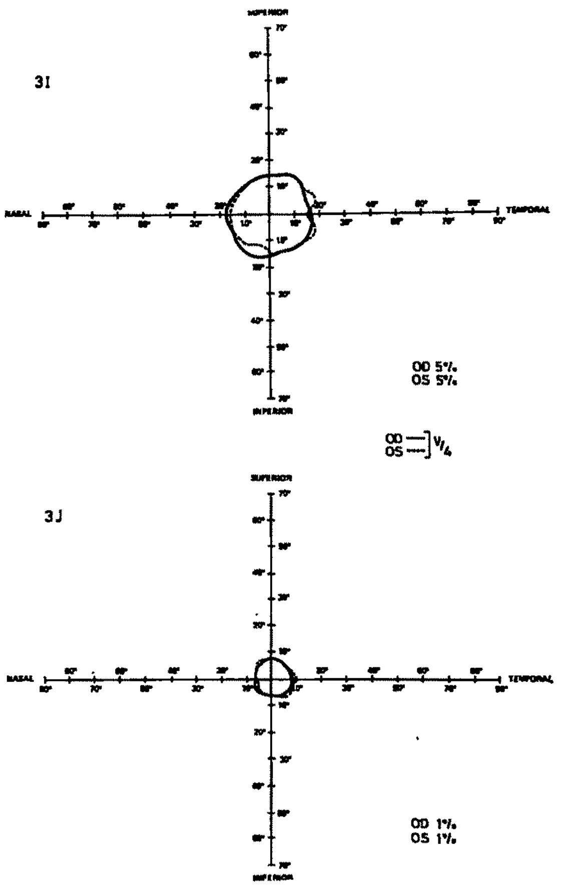
The numerical value for visual field area of the right eye is plotted against the numerical value for visual field area of the left eye, for each patient, in Fig. 4. If perfect bilateral symmetry were obtained, all the data points would fall on the diagonal line. The calculation of the product moment correlation yielded a nearly perfect correlation coefficient ($r=0{\cdot}96$). Thus, visual field area loss in the right eye parallels to a high degree the visual field area loss in the left eye.

ABSOLUTE THRESHOLD PROFILES

The mirror image of the sensitivity profile for the left eye was plotted along with the sensitivity profile for the right eye for each patient. As exemplified in Fig. 5, not only does the loss of sensitivity occur to about the same degree in each eye, but also the shapes of the sensitivity profiles are quite similar. These data complement the visual field data plotted in Fig. 3. A comparison of the data from patients with RP with normal values (Fig. 5L) demonstrates a 1·0 to 2·0 log unit loss in foveal sensitivity for all patients.

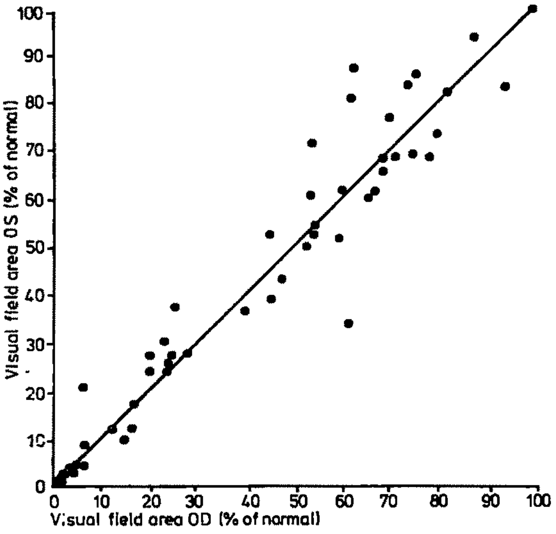
Discussion

We found a high degree of bilaterial symmetry in loss of visual function in patients meeting the criteria of typical RP, independent of the mode of



Figs 3i, 3j

Fig. 4 *Visual field area expressed as a percentage of the normal visual field area for the right eye is plotted against the visual field area for the left eye for each patient (points)*



inheritance. This statement holds true for visual acuity, colour discrimination, kinetic visual fields, and static absolute threshold profiles. Such bilateral symmetry, in both the extent and pattern of loss of visual function, complemented by Biro's (1963) finding of symmetry in fundus pigmentation, suggests a high degree of congruence in the pattern and natural history of the retinal degeneration.

The finding of a high degree of symmetry in RP is important from the standpoint of evaluating therapy which employs one eye as a control (for example, Berson's (1971) total light exclusion trial) and for better understanding the natural course of RP. The symmetry in the pattern of vision loss (see Figs. 3 and 5) suggests that the progression follows morphological features yet to be identified. We are at present examining this suggestion in more detail.

A consistent observation in the present study was the presence of disorders of foveal vision at all stages of RP progression, as evident in the measures of colour discrimination and absolute foveal thresholds. Previous investigators have made similar observations (Zeavin and Wald, 1956; Sunga and Sloan, 1967; Adams *et al.*, 1972), but such foveal abnormalities have been overshadowed by the usual persistence of good visual acuity until late in the course of RP. As shown in Fig. 6, we observed a high correlation between the colour error score and reduction in the area of visual field ($r=0{\cdot}73$). These results indicate that progression in loss of foveal colour discrimination is parallel to the loss of visual field.

In conclusion, we have found that bilateral symmetry in loss of visual function is a characteristic feature of typical RP. Also, from the high degree of congruence in visual fields and threshold profiles,

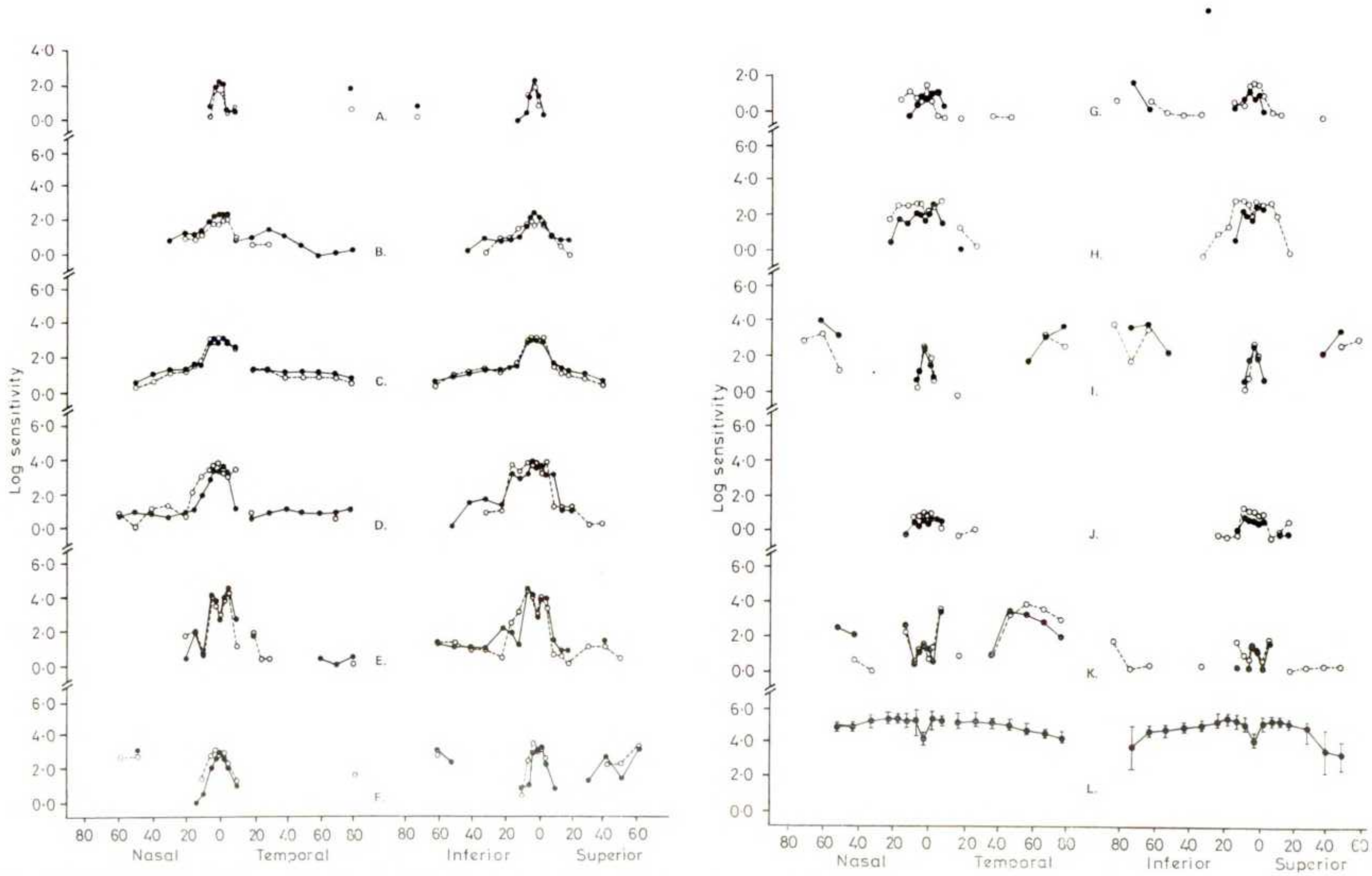


Fig. 5 *Absolute thresholds along the horizontal (left side) and vertical (right side) meridians are plotted for representative examples of retinitis pigmentosa patients (A–K). Right eye data (closed circles) are compared with left eye data (open circles) for each patient. The means of 5 normal observers are plotted in figure 5L (points). The error bars represent the total range of normal values*

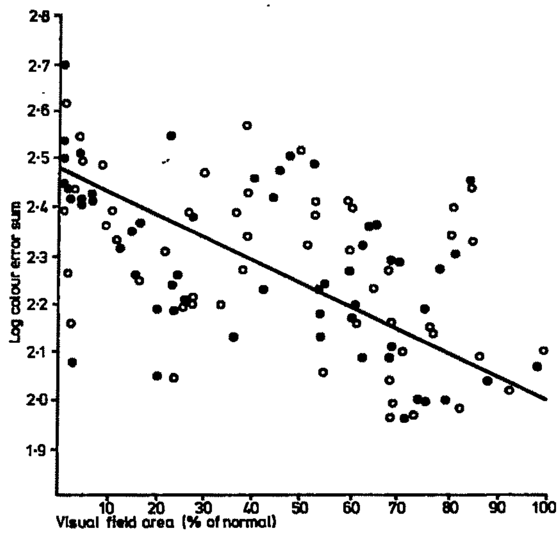


Fig. 6 *Log colour error sum is plotted against percentage of normal visual field area for each patient. Closed circles represent data for the right eye and open circles represent data for the left eye. The best-fit line from a linear regression analysis is plotted along with the data points*

we conclude there is symmetry in the *pattern* of visual function loss. The high correlation between loss of foveal colour discrimination and loss of visual field implies the existence of a bilaterally symmetrical, progressive, diffuse component to the RP mechanism that similarly affects both foveal and peripheral visual function.

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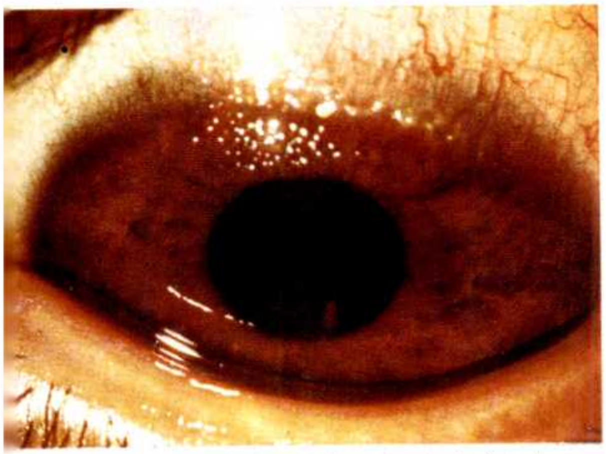
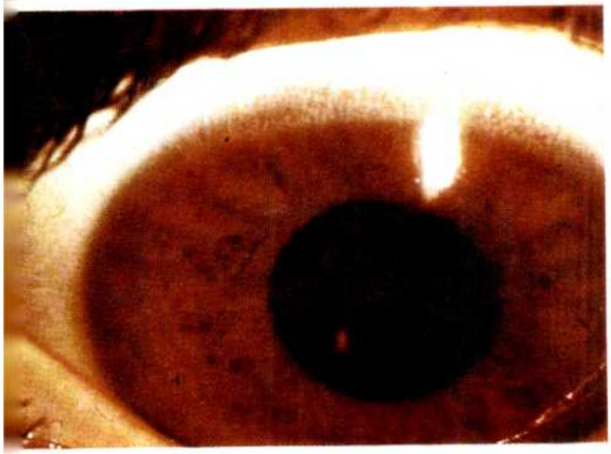


The superior limbus in a placebo treated eye of a patient suffering from rnal kerato-conjunctivitis, stained with fluorescein. Note the limbal peraemia and swelling and the irregularity of the corneal surface.



The opposite eye of the same patient treated with sodium cromoglycate e drops. Before treatment, both eyes appeared similar.

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Cryotherapy of proliferative sickle retinopathy, II: triple freeze-thaw cycle

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From the Sickle Cell Eye Clinic, University of Illinois Eye and Ear Infirmary, Chicago

SUMMARY Complete closure of retinal neovascularisation due to proliferative sickle cell retinopathy was achieved in 28 'sea fans' (areas of neovascularisation) in 9 eyes of 9 patients by means of a triple freeze-thaw technique. However, 2 eyes developed subsequent rhegmatogenous retinal detachments, presumably related to vitreous traction on necrotic retina. We therefore recommend photocoagulation as the best treatment of proliferative sickle cell retinopathy. If opacities in the media prevent photocoagulation, a single freeze-thaw cycle is preferable.

Persons with sickle cell anaemia (haemoglobin SS), sickle cell B thalassaemia (haemoglobin S-Thal), and especially sickle cell haemoglobin C disease (haemoglobin SC) develop vasoproliferation from the retina into the vitreous. Left untreated, these areas of neovascularisation (sea fans) may progress to vitreous haemorrhage, tractional retinal detachment or rhegmatogenous retinal detachment (Goldberg, 1971). Photocoagulation with the xenon arc or argon laser has been used to destroy neovascular tissue (Goldberg and Acacio, 1973; Goldbaum *et al.*, 1977). For successful photocoagulation the media must be sufficiently clear over the feeding vessels to allow the photocoagulation beam to form a sharp image in the retina. Vitreous haemorrhage or other opacities in the media can prevent successful photocoagulation. Furthermore, photocoagulation has known complications such as haemorrhage (Goldbaum *et al.*, 1977), choroidal ischaemia (Goldbaum *et al.*, 1976), and choroidovitreal neovascularisation (Galinos *et al.*, 1975; Goldbaum *et al.*, 1977). A previous paper from our clinic relates our experiences with a single freeze-thaw cycle of transconjunctival cryopexy in the treatment of proliferative sickle retinopathy (Lee *et al.*, 1975). Thirteen sea fans in 10 eyes of 6 patients were treated. Four of these 13 sea fans (31%) were still patent, though markedly attenuated, after treatment. None of the attenuated sea fans has bled in the 3 years since the cryopexy.

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Several authors have reported successful treatment of retinoblastomas and vascular tumours, such as retinal angiomatosis, with repeated freeze-thaw techniques (Hale and Christensen, 1968; Amoils and Smith, 1969; Welch, 1970; Watzke, 1973; Watzke, 1974). With this in mind an attempt was made to improve our previous cryotherapeutic results in proliferative sickle retinopathy by employing a triple freeze-thaw cycle.

Materials and methods

Between February 1974 and July 1974 every third eye of the patients seen at the Sickle Cell Eye Clinic of the University of Illinois Eye and Ear Infirmary that required treatment for proliferative sickle cell retinopathy and any eye in which sea fans could be identified but were partially obscured by vitreous haemorrhage were selected for triple freeze-thaw cycle cryotherapy. A total of 28 sea fans in 9 eyes of 9 patients were treated. The patients' ages ranged from 16 to 53 years, with a mean of 30 years. Seven patients had haemoglobin SC, 1 had haemoglobin SS, and 1 had haemoglobin AS (all confirmed by quantitative haemoglobin electrophoresis).

Before treatment each patient received an eye examination with measurement of best corrected visual acuity, slit-lamp examination, and a detailed retinal drawing with indirect ophthalmoscopy and scleral depression. Fluorescein angiography confirmed the patency of the sea fans to be treated. In eyes in which vitreous haemorrhage made identification of a sea fan difficult or uncertain, fluorescein angioscopy with a Wratten 47 blue filter on an indirect ophthalmoscope was performed to locate the telltale green vitreous cloud of fluorescein overlying each sea fan.

Each treatment was performed either with a carbon dioxide probe or a fluorocarbon probe, each adjusted for maximum cooling. The intense cryopexy was painful with topical anaesthesia. Hence 1% lignocaine was injected subconjunctivally in the quadrant to be treated, or a retrobulbar injection was given. The cryoprobe was applied to the globe directly over the site of the smaller sea fans, which were then treated with a triple freeze-thaw that totally encompassed the area of neovascularisation. Larger sea fans were first treated with a triple freeze-thaw cycle to the feeding vessels. The cryoprobe was then moved to adjacent sites until the entire sea fan had been covered (Fig. 1).

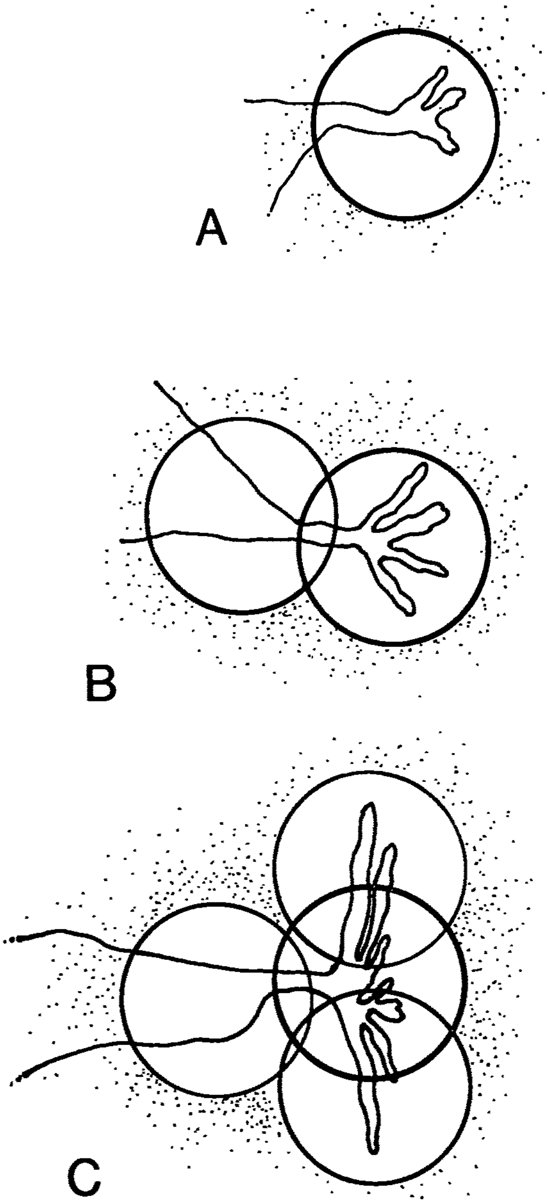

Fig. 1 *Technique of triple freeze-thaw cryopexy. For a small sea fan (A) a single site was treated. For a somewhat larger lesion (B) the feeding vessels were treated first, followed by freezing of the lesion itself. For a large sea fan (C) the feeding vessels were treated and then multiple applications were made to cover the entire lesion*

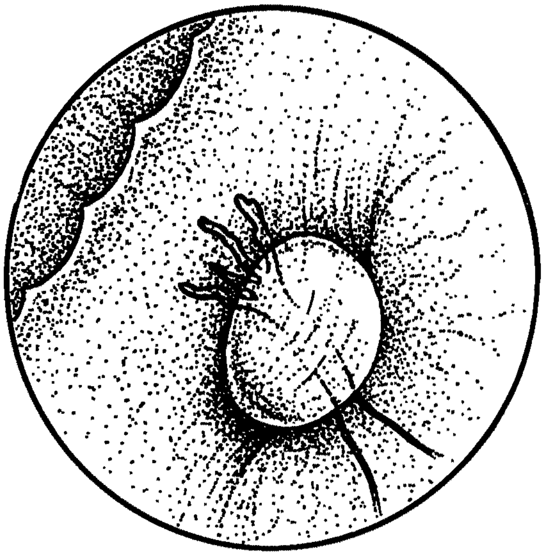

Fig. 2 *Endpoint of treatment corresponded to incorporation of vessels within the iceball with a 'frosted' appearance to the vessels*

Each transconjunctival cryopexy lesion was monitored by indirect ophthalmoscopy. The probe was positioned to indent the desired area. The iceball was allowed to grow until the treated vessels were incorporated. The end point was a hazy appearance of the vessels to be treated within the iceball as if they were being viewed through frosted glass (Fig. 2). The process was repeated two additional times at each site of application. It is important to note that, when the vessels to be treated stood out brilliantly in relief against the white background of the iceball, the iceball had not yet reached the vessels and the end point had not yet been achieved. When vitreous haemorrhage was present and the view of the sea fan was obscured, the end point was more difficult to identify and had to be estimated.

Twenty-four or 48 hours after treatment and again several weeks later fluorescein angiography was

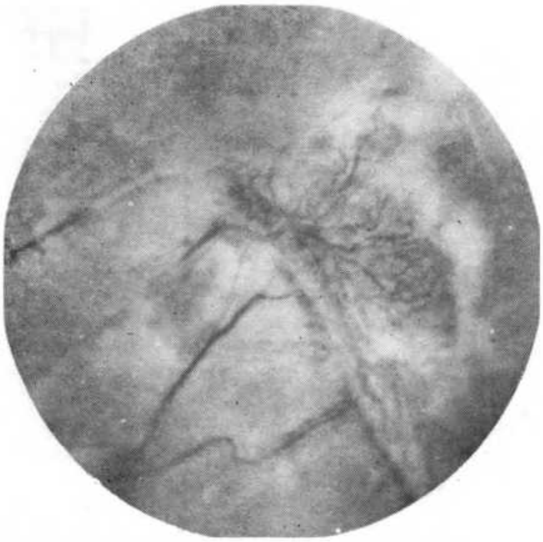

Fig. 3 *Appearance of treated sea fan 1 day after cryopexy*

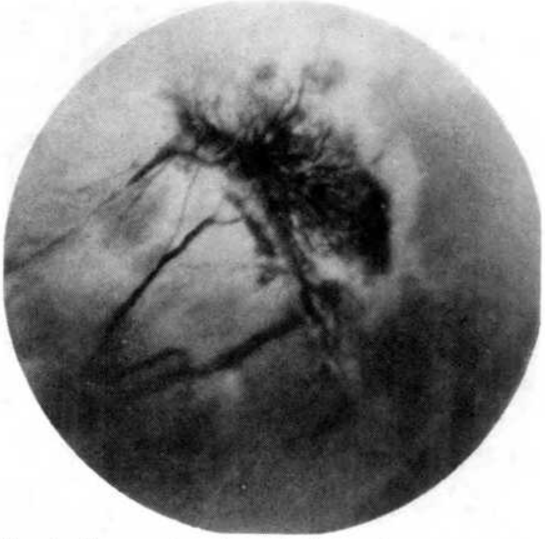

Fig. 4 *Fluorescein angiography 1 day after treatment shows absence of perfusion*

performed to determine if the treated sea fan was perfused.

Results

After this intense cryopexy there was often considerable transient conjunctival chemosis. Blood vessels in the conjunctiva were sometimes occluded 24 to 48 hours after the treatment. After a week the conjunctiva appeared normal. No abnormalities in muscle balance were induced.

After the triple freeze-thaw applications each of the sea fans was engorged and appeared purple against a background of pale oedematous retina (Fig. 3). Fluorescein angiography 24 or 48 hours later showed non-perfusion of the treated sea fan (Fig. 4); all 28 sea fans were closed and have not reperfused over a 3-year period of observation (Fig. 5, Table 1).

In 2 of the 3 eyes with vitreous haemorrhage (Cases 2 and 4) the vitreous cleared spontaneously over the next 6 months. One patient (Case 5) with a dense central vitreous haemorrhage failed to clear over a 6-month period, though there was no evidence of rebleeding. Vitrectomy and subsequent lens extraction returned the visual acuity to 20/20 with a soft contact lens.

Two of the patients (Cases 1 and 8) developed local rhegmatogenous retinal detachments shortly after treatment. These detachments were successfully treated by scleral buckling with cryopexy. In both these eyes a retinal hole appeared to have been pulled open by vitreous traction on retina made necrotic by the triple freeze-thaw cryopexy.

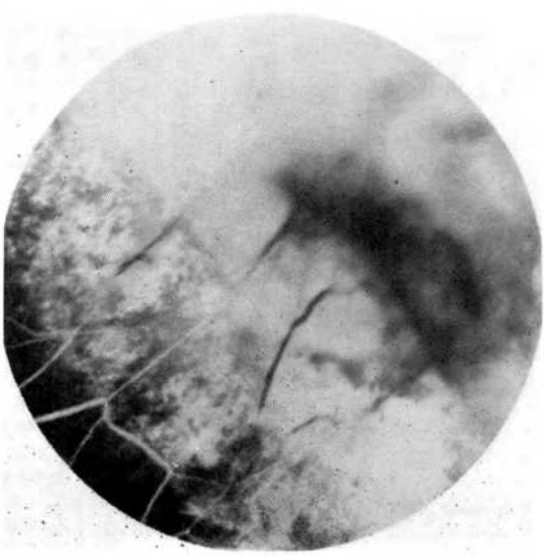

Fig. 5 *Fluorescein angiography some weeks later again shows absence of perfusion of treated lesion*

Discussion

Multiple freeze-thaw cycles have certain theoretical advantages in the destruction of tissue over a single freeze cycle. Zacarian (1977) showed that 2 freeze

Table 1 *Triple freeze-thaw cryotherapy of proliferative sickle retinopathy*

Patient	*Haemoglobin type*	*Age at time of treatment (years)*	*Eye treated*	*Site of sea fan (clock hours)*	*Pre-op. visual acuity*	*Final visual acuity*	*Comments*
1	SC	20	R	0300 0800	20/30	20/40	Developed retinal detachment; successfully repaired
2	SC	24	R	0700 0800 0830 0900 1030	CF 3 ft	20/25–3	Vitreous haemorrhage prevented photocoagulation
3	SC	25	L	0200 0300 1100 1200	20/25	20/25	
4	SC	26	R	0200 0300 0900 1000 1130	LP with projection	20/25	Vitreous haemorrhage prevented photocoagulation
5	SC	31	R	0300 1200	HM	20/20	Vitreous haemorrhage prevented photocoagulation. Vitrectomy and lens extraction were subsequently performed
6	SC	34	L	0200 0330	20/25	20/25	
7	SC	53	R	0300 1200	20/30	20/40	
8	SS	16	R	0800	20/30	20/25	Developed retinal detachment; successfully repaired
9	AS	39	L	0200 0300 1000 1100 1130	20/25	20/50	

cycles are far more lethal to suspended HeLa cells than a single cycle, and he concluded that a period of incomplete thaw permitted 10% more cells to remain viable than did a complete thaw between freezes. In experimental retinal cryopexy lesions in albino rabbits Amoils (1969) noted that a triple freeze-thaw cycle potentiated vascular damage and accelerated and intensified the exudation, stasis, and thrombosis present in such lesions. He showed that with a triple freeze-thaw technique the vascular stasis became marked within 20 minutes and involved larger choroidal veins and arteries throughout the lesion. Petechiae, presumably secondary to minute ruptures of the capillary walls, were noted on the surface of retinal angiomata and retinoblastomas treated with a triple freeze-thaw cycle, but in no case did bleeding extend into the vitreous.

In the current study complete closure of 28 sea fans was achieved with a triple freeze-thaw cycle. Unfortunately 2 of the 9 eyes treated by this method developed retinal detachments. From our experience with photocoagulation, single freeze-thaw cryopexy, and triple freeze-thaw cryopexy we consider that photocoagulation is the safest and preferred treatment for closing the circulation to a sea fan. We have discontinued triple freeze-thaw cryopexy because of the occurrence of the 2 retinal detachments. The vitreous traction that is almost invariably present with proliferative sickle retinopathy makes triple freeze-thaw cryopexy too risky. When vitreous or lenticular opacities prevent photocoagulation, but allow identification and partial visualisation of sea fans, single freeze-thaw cryopexy is an acceptable alternative to photocoagulation. Though single freeze-thaw cryopexy is not 100% effective in closing treated sea fans, none of the attenuated sea fans that were not totally closed has bled after treatment (Lee *et al.*, 1975).

We would like to thank Drs George Asdourian, Krishan Nagpal, Dimitri Patrianakos, and Chang-Bok Lee for their assistance in the care of these patients.

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Solar keratosis, pterygium, and squamous cell carcinoma of the conjunctiva in Malawi

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SUMMARY The histological features of 234 conjunctival biopsies from Africans in Malawi have been re-examined. The appearances of solar keratosis, pinguecula, and pterygium are presented as part of a continuous spectrum of the same pathological process and aetiology, which may lead to carcinomatous change. The results are discussed with regard to the specific geographical distribution of such lesions found by other workers, with particular emphasis on ultraviolet radiation as the main aetiological factor.

Squamous cell carcinoma of the conjunctiva is more common in Africa than in temperate climates (Templeton, 1967; Ticho and Ben-Sira, 1970; Daoud and Osman, 1970; Maertens and Blodi, 1972). It has been suggested that these tumours arise from pre-existing lesions which are the result of prolonged exposure to ultraviolet light. These lesions are usually classified as a pinguecula or pterygium by ophthalmologists and are characterised by a wedge-shaped opaque thickening near the limbus which may extend on to the cornea from the scleral conjunctiva. Histopathologists usually describe such lesions as solar keratosis and often comment on the degree of epithelial atypicality or dysplasia. However, Cameron (1965) does not emphasise epithelial changes or a liability to carcinomatous change. With these problems in mind we have re-examined the histological features of 224 conjunctival biopsies from Africans in Malawi. The results are discussed in the light of observations from several geographical locations.

Materials and methods

Since 1968 diagnostic histopathology for all hospitals in Malawi has been undertaken by the Department of Morbid Anatomy, St. Thomas's Hospital Medical School, London. All biopsies and removed surgical specimens are fixed in 10% formalin and are then forwarded to the Central Laboratories in Blantyre. They are then dispatched in weekly batches by air to London, where they are processed and sectioned.

During this period the number of ophthalmologists in Malawi has varied, and specialist attention is not available throughout the country. The proportion of conjunctival lesions from which biopsy specimens have been taken and sent for histological examination has also varied. The numbers of cases reported here do not therefore give any idea of the true incidence or prevalence of these conditions. They are, however, recognised as a common problem in ophthalmic practice.

All biopsy and surgical material from Malawi is coded according to the Standardised Nomenclature of Pathology. Reports coded for eye or orbit were extracted and the slides from all lesions involving the conjunctiva were reviewed. In some cases extra sections were cut and stained with elastin-Van Giesen's stain. Each biopsy was assessed for degenerative and inflammatory changes in the subepithelial connective tissues and for abnormalities of the squamous epithelium and melanocytes.

Results

The clinical information was limited in many of these cases, but the great majority of conjunctival biopsies had been diagnosed either as pterygium or pinguecula (Fig. 1), though the criteria for this differentiation were not constant. There were also some patients with a clinically invasive carcinoma (Fig. 2) and a few with other lesions such as papilloma.

HISTOPATHOLOGY

The main histological features and the diagnosis are shown in Tables 1 and 2; 167 lesions were reclassified as 'solar keratosis' with varying degrees of

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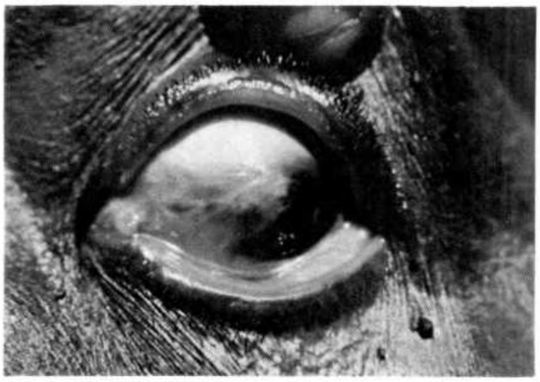

Fig. 1 *A typical precancerous lesion (pterygium) extending on to the cornea*

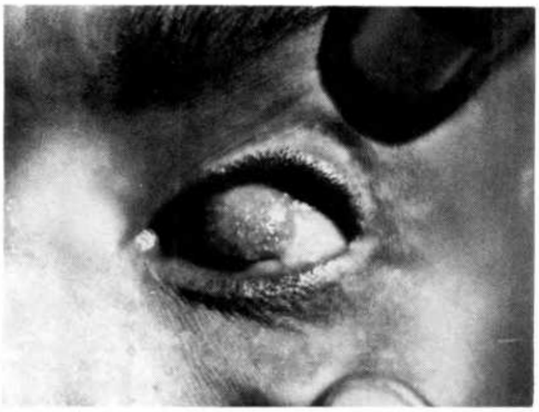

Fig. 2 *Squamous cell carcinoma with invasion of corneal tissues*

epithelial abnormality, 54 as invasive carcinomas, and in 13 there was difficulty in assessing the nature of the lesion; several of these were considered to be 'microinvasive' carcinomas.

SUBEPIDERMAL CONNECTIVE TISSUES

Changes similar to those seen in the skin in senile or solar keratosis were present in 163 out of the 167 lesions which were finally classified as solar keratosis. They are characterised by fragmentation and elastotic degeneration of collagen fibres, often with accentuation of their eosinophilia and, sometimes, with foci of collagen necrosis (Fig. 3). In microinvasive carcinomas these connective tissue changes were evident in the same section in only 8 out of 13 cases and in those with frankly invasive carcinomas in 17 out of 37 cases. In the latter it was evident that there was a desmoplastic reaction to the infiltrating tumour, and this may have obscured the degenerative changes.

CHANGES IN THE SQUAMOUS EPITHELIUM

Some abnormality of the epithelium was present in all but one of the 167 lesions. These were graded according to the degree of abnormality (Table 1).

HYPERPLASIA AND MILD DYSPLASIA

In this group of 126 cases the squamous epithelium was of normal thickness or only slightly hyperplastic

Table 1 *Histological findings in non-invasive lesions (solar keratosis)*

	Connective tissue	
Epithelium	*Normal*	*Degeneration*
Normal	0	1
Hyperplasia or mild dysplasia	0	126
Moderate dysplasia	3	16
Marked dysplasia or carcinoma *in situ*	1	20
Total 167		

Table 2 *Histological findings in doubtful or microinvasive and infiltrating carcinomas*

	Connective tissue	
	Reactive	*Degenerative*
Doubtful or microinvasive	5	8
Infiltrating	37	17
Total 67		

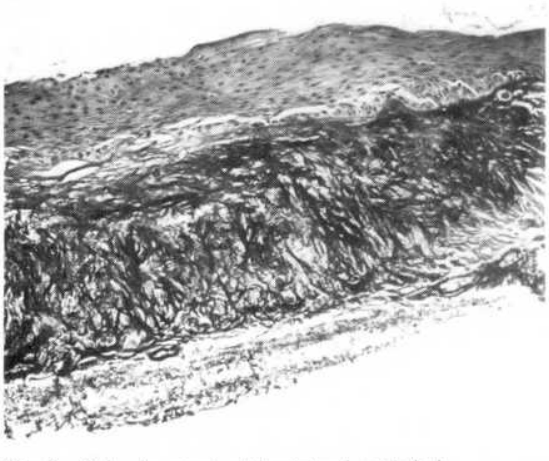

Fig. 3 *Solar keratosis with minimal epithelial abnormality and marked solar degeneration of subepithelial connective tissues. Haematoxylin and Van Giesen (× 77)*

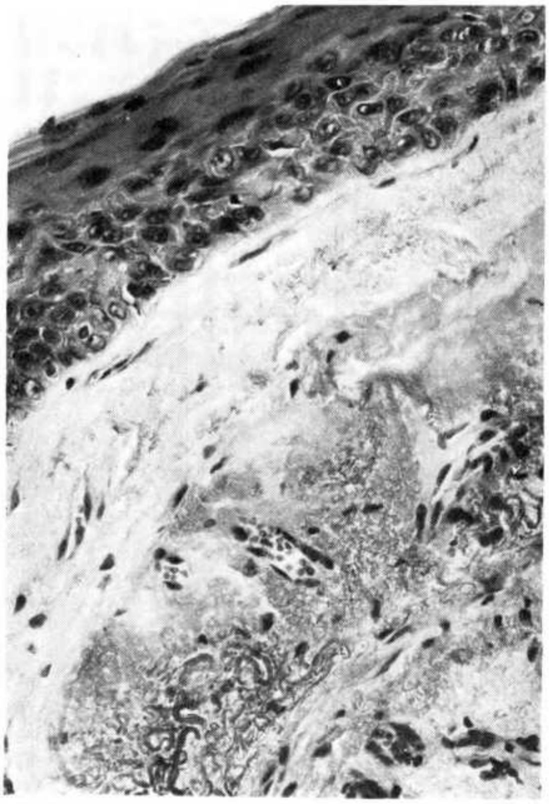

Fig. 4 *Solar keratosis with connective tissue degeneration and mild epithelial dysplasia. Haematoxylin and eosin* (× 240)

due to acanthosis. There was a variable keratinisation of the superficial cells, often associated with some abnormality of cell maturation and minor degrees of cell atypia or loss of polarity, which did not exceed a quarter of the total epithelial thickness (Fig. 4). In some biopsies there was spongiosis of the epithelium associated with subepithelial oedema or chronic inflammatory cell infiltration. The clinical and pathological features of this group correspond closely to the definition of pterygia (Cameron, 1965), though some ophthalmologists would refer to a number of the lesions as pingueculae (Ticho and Ben-Sira, 1970).

MODERATE DYSPLASIA

This group of 19 cases was characterised by distinct abnormalities of epithelial maturation, with loss of cellular polarity, the presence of abnormal cells with an increased nuclear-cytoplasmic ratio, dyskeratosis of focal cells, and a variable keratinisation (Fig. 5). The abnormal cells did not, however, extend to the surface and usually occupied less than three-quarters of the total thickness of the epithelium. Rete ridges were not a feature and the basal layer was unbreached. The features in some biopsies were leucoplakic in pattern.

MARKED DYSPLASIA AND CARCINOMA IN SITU

All the lesions in this group of 21 cases showed marked disturbances of cell maturation, polarity, and nuclear size; and mitoses, often abnormal, were seen (Fig. 6). In some specimens large and atypical nuclei as found in Bowen's disease of the skin were seen, and all showed whole-thickness abnormality, though keratinisation was a variable feature. Occasionally cells were arranged in whorls, giving the appearance of a cell nest. The basal layer of cells, though abnormal, was intact and sometimes showed ridging.

MICROINVASIVE CARCINOMA

In 13 biopsies the possibility of early carcinomatous change was considered. In some there were clear-cut small foci of invasion (Fig. 7). In others the basal layer was irregular, and assessment of early infiltration was obscured by oedema and inflammation.

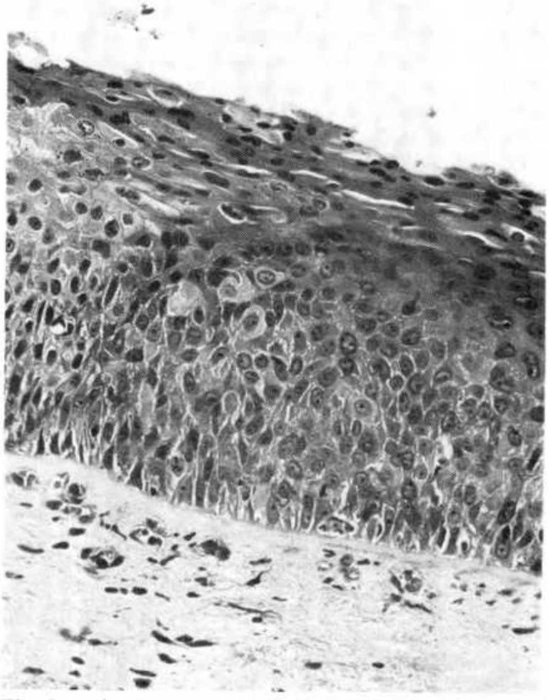

Fig. 5 *Solar keratosis with moderate epithelial dysplasia more evident on the right of the picture. Haematoxylin and eosin* (× 250)

INFILTRATING SQUAMOUS CELL CARCINOMA

All cases in this group of 37 cases showed frank invasion (Fig. 8), and in many there was extensive destruction of the eye, with a fungating and ulcerated lesion. Some tumours were very well differentiated, with much keratinisation, but a few were poorly differentiated.

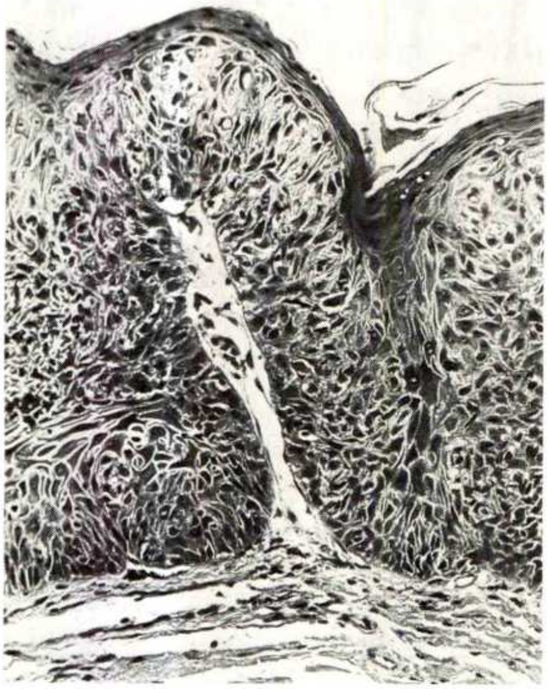

Fig. 6 *Carcinoma* in situ *of conjunctiva. Haematoxylin and eosin* (× 200)

CHANGES IN PIGMENT CELLS

A feature of many of these lesions was an abnormal proliferation of melanocytes. These cells contain pigment arranged in long dendritic processes extending between the squamous epithelial cells (Fig. 9) and were often seen throughout the lesion. Pigment was also often present in the squamous cells. The proportion of melanocytes to squamous epithelial cells was estimated in each biopsy and given an arbitrary score. The scores were averaged for each group as shown in Table 3. Melanocytic hyperplasia was maximum in lesions with severe dysplasia and was also often present in infiltrating carcinomas.

Ten cases of conjunctival papilloma were seen during the period of investigation and none showed precancerous changes. There was no evidence to support the idea that carcinoma of the conjunctiva arises in pre-existing benign lesions of the papillomatous type (Goldberg *et al.*, 1963).

Discussion

NOMENCLATURE AND PATHOLOGY

In an earlier paper from Malawi, Ticho and Ben-Sira (1970) described the clinical and pathological features of lesions in the bulbar conjunctiva close to the limbus occurring in the African population. They described 3 clinical groups:

(1) Pinguecula (25 cases). These are localised yellowish-white swellings without keratinisation. On histological examination, there is subepithelial

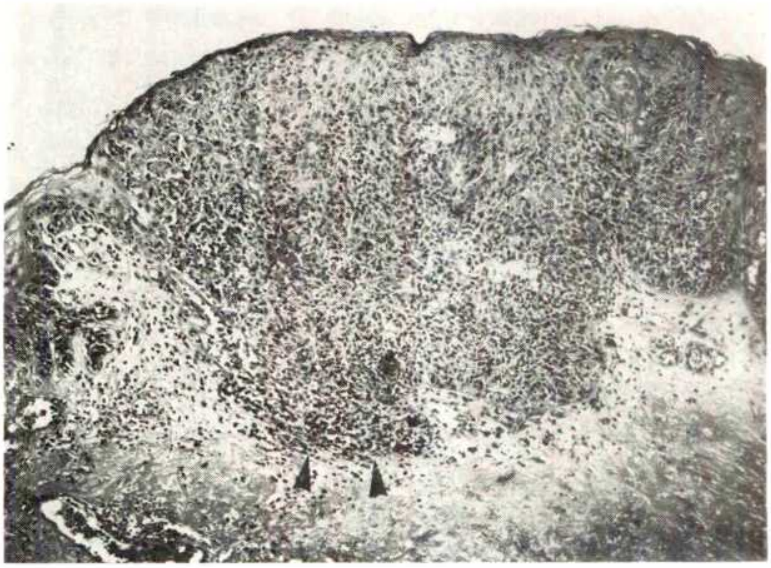

Fig. 7 *Microinvasive carcinoma. The arrow indicates an area where the epithelium is invading connective tissues. Haematoxylin and eosin* (× 210)

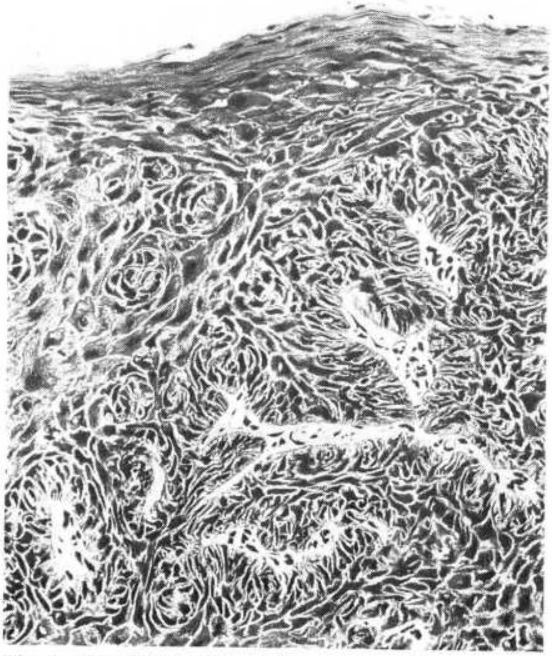

Fig. 8 *Invasive squamous cell carcinoma. Haematoxylin and eosin* (× 190)

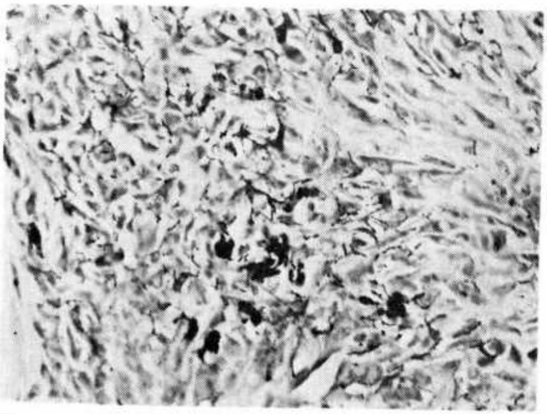

Fig. 9 *Melanocytic hyperplasia with dendritic processes extending between squamous cells in a patient with carcinoma* in situ. *Fontana's silver technique* (× 180)

stromal degeneration, with minimal epithelial change apart from acanthosis.

(2) Elevated white glistening lesions surrounded by pigment. These showed 3 histological subgroups: simple epidermalisation with hyperkeratosis and rete peg formation (22 cases); leucoplakia with more advanced dyskeratosis (36 cases); and Bowen's type of precancerous change (12 cases).

Table 3 *Melanocytic hyperplasia in solar keratosis and in carcinoma of the conjunctiva*

Epithelium	*Melanocytes*
Normal	2·0
Mild dysplasia	4·1
Moderate dysplasia	4·4
Severe dysplasia	5·4
Carcinoma *in situ*	2·5
Well differentiated carcinoma	3·1
Moderately differentiated carcinoma	2·2
Poorly differentiated carcinoma	—

(3) Fleshy protruding lesions of an invasive nature, often pink or red and papillomatous or cauliflower in shape (8 cases), which were all invasive squamous cell carcinomas.

Martens and Blodi (1972) described epibulbar lesions in Africans from Zaire. They differentiated pingueculae which are elevated, whitish lesions at or near the limbus from pterygia, which they describe as soft elevations with a smooth surface surrounded by blood vessels and fixed to the limbus. Hogan and Zimmerman (1966) suggest that when there is nuclear atypicality and dyskeratosis in either a pterygium or a pinguecula the additional term 'active keratosis' may be used. Sevel and Sealy (1969) identified 3 major groups: pterygia, defined as 'a degenerative and hyperplastic process in which there is encroachment of the bulbar conjunctiva onto the cornea' (this category loosely included pingueculae); carcinoma *in situ* (which is equated with Bowen's disease); and invasive carcinoma. The criteria were based solely on the histopathological appearance, and they found no absolute correlation with the clinical features.

All these lesions have features which are seen in damage by solar irradiation, and the covering of the eye is 1 site in an African which is not protected from this effect by pigmentation. It has been observed that carcinomas of the conjunctiva arise more frequently on the medial aspect of the conjunctiva in the interpalpebral fissure. This localisation may be related to the mechanism of sunlight-induced blepharospasm (Sevel and Sealy, 1969).

Our findings suggest that the lesions, which are nearly all associated with solar damage to subepithelial connective tissues, represent a continuous spectrum of epithelial abnormality from slight acanthosis and hyperkeratosis through mild and moderate dysplasia to severe dysplasia and carcinoma *in situ*. Inevitably in a biological phenomenon there is some variation in the type and degree of response, and this can account for patterns labelled as epidermalisation, leucoplakia, or Bowen's disease. Similar histological variations occur in precancerous lesions of the skin and cervix, and it is not possible to demonstrate an absolute correlation between the histopathological abnormality and the biological potential of the lesion. In reporting the histology of these lesions we suggest that the term 'solar keratosis' be used and qualified by the degree of epithelial abnormality as mild, moderate, or severe dysplasia, or carcinoma *in situ*.

The microinvasive and infiltrating carcinomas showed a variable degree of squamous differentiation. However, whereas the classical type of carcinoma *in situ* could be envisaged as the predecessor of a poorly differentiated tumour, the preinvasive histology of a well differentiated tumour remains uncertain.

Proliferation of dendritic melanocytes among the atypical squamous epithelial cells was a common finding, particularly in moderate and severe dysplasias, and sometimes this feature had led to a clinical diagnosis of cellular naevus or malignant melanoma. No cases of malignant melanoma of the conjunctiva were seen during the period under review. Some focal pigmentation may be seen in normal African conjunctivae, and it seems possible that the melanocytic hyperplasia represents a protective response.

Most authors suggest that these various lesions, whatever terminology is used, represent different stages of a process resulting in some patients in the development of an invasive carcinoma. The high frequency of solar keratosis (pterygia) of the conjunctiva in Africans is associated with a high incidence of squamous cell carcinoma, which suggests that they are precancerous. Zimmerman (1964) emphasised that carcinoma rarely arose in the epithelium overlying pterygia or pingueculae. However, solar keratosis of the skin does not invariably lead to invasive carcinoma, nor are dysplastic lesions in other sites, such as the cervix, always progressive.

EPIDEMIOLOGY AND AETIOLOGICAL FACTORS

The higher frequency of these lesions in Africans living in the tropics may be accounted for by increased exposure to ultraviolet light, though, as Maertens and Blodi (1972) point out, the humidity is often high and ultraviolet rays are readily absorbed in a humid atmosphere. Cameron (1965) found a good correlation between latitude and pterygium rates:

Pterygium rate		*Latitude*
Low	(0–1·9%)	40°
Moderate	(2–4·9%)	35°–40°
High	(5–10%)	30°–35°
Very high	(10% or more)	30°–equator

He held the view that the incidence of pterygium is highest in areas where the sun is at an angle of 80° or more for the larger part of the year. Thus, in such areas, the populations are exposed to ultraviolet rays of wavelength from 3200 Å to 2900 Å (320 to 290 nm). In areas where the wavelengths are in the band below 2900 Å the prevalence of pterygium is relatively low, and this is correlated with the oblique angle at which the rays fall.

The prevalence of pterygia in countries between the Equator and the 30th parallel such as North India and Pakistan, Mexico, the Central American States, and the West Indies agrees well with the expected rates. Similarly, most of Europe, Asia, and Canada, which lie north of the 40th parallel, have a low rate. There are some parts of the world (mainly islands) where the pterygium rate is about 20% or more, e.g., Hawaii, Samoa, Marshall Islands, Aitutaki, and Aruba. This may be due to reflection of ultraviolet light from the sea.

However, Parthasarathy and Gupta (1967) do not think Cameron's theory can explain the wide variation in the prevalence rates in different states of rural India. Pterygium is common in the states of Maharashtra, Andura, and Pradesh, but Madras, and especially Kerala, which are nearer the Equator, have a lower incidence. Moreover, there are other discrepancies between the theoretical world distribution based on latitude (Cameron, 1965) and the actual distribution. Thus Rasanayagam (1973) reports that the prevalence of pterygium in West Malaysia is 7·4% whereas the expected theoretical prevalence for an area between 0° and 4° N should be over 10%. Other exceptions to the relationship with latitude are found in Borneo, Java, and New Guinea, whose actual pterygium rates are lower than expected, with some parts of New Guinea under 5%. However, in the mainland area of New Guinea the prevalence of pterygium is higher in the coastal lowlands and lowland savanna than in the lowland rain forest (Vines, 1970). Sivasubramaniam (1970) also has figures for Ceylon which do not agree with Cameron's hypothesis. Ceylon lies between 6° and 10° N latitude, and according to Cameron the theoretical expected rate for pterygium in Ceylon should be more than 10%. However, Sivasubramaniam found a prevalence of only 0·7%. He postulated that the thick and luscious vegetation carpeting the whole land, the absence of deserts, the fanning of the land by 2 monsoons, which bring rain-bearing clouds to the central hills rising to a height of 9000 ft (2700 m) above sea level are all mitigating factors. The ample cloud cover and vegetation cut down the ultraviolet radiation.

Nearly all observers have found that there is a higher incidence in men than women and an increasing incidence in age from 20 to 50 years. In North Malaysia a study was conducted on Malays, Indians, and Chinese. In the former 2 groups the sex ration was 3:1 male:female, but in the Chinese the male preponderance was less (10:7, male:female). This might be due to the Chinese women leading a more active outdoor life. The incidence in fishermen is much higher than in the general population, and that in Chinese fishermen is more than in Malays (Rasanayagam, 1973). It is interesting and perhaps not wholly surprising that in Ceylon two of the high incidence areas are coastal, and here the occupation of the populace is fishing. However, two other coastal areas (Jaffra and Bathirla) where fishing is the livelihood show a low incidence of pterygium (Sivasubramaniam, 1970).

There is a little evidence for ethnic variations in the prevalence rates of pterygia. Ash (1950) reported a higher incidence in blacks than whites in America. Ida Mann (1962) in her surveys of whites, full bloods, and coloured people in West Australia emphasised that there is a much higher prevalence among the full bloods and coloured people than in the whites. She has deduced from the physical characteristics and sagas and legends of the aborigines (= original Australians) that they have come from the Dravinian Hill tribes in South India. Indeed, the Dravinian races of South and East India are noted for their high incidence of pterygium. In the study in West Malaysia the highest racial prevalence is found in the Chinese. The majority of Indians in Malaysia are immigrants from South India, and this group had a lower prevalence than other ethnic groups (Rasanyagam, 1973). This might be due to the inclusion of Ceylonese in the Indian group, which would tally with the low incidence of pterygium found in Ceylon by Sivasubramaniam (1970).

Youngson (1972) reviewed 5000 Arabs in Jerusalem of whom 460 (9·2%) had true pterygium; 298 patients had unilateral pterygia, of which 183 were in the left eye and 115 in the right eye, a significant difference. An ingenious theory was postulated by Batten (1972), who considers that this may be due to shading of the right eye with the right hand. An unusual feature of Youngson's study was the observation that the lesions regressed in old age.

Some workers, including Scarpa (1880), Gerundo (1951), and Friede (1949), believed that chronic bacterial or catarrhal conjunctivitis initiates the progress. Stellwag-Carion . (1880) suggested that pterygium may develop from an ulcer caused by herpes virus. Poncet (1880) thought that 'vibrions' were responsible and claimed to have seen spores in the tissue of the pterygium head. Other workers have suggested that trauma, vitamin A deficiency, or the installation of native medicines may play a role. There is no good epidemiological evidence to support any of these as major factors in the pathogenesis of such lesions. Elliot (1966) suggested that ultraviolet light caused drying of the tear film and that this was followed by pterygium. Goldberg and David (1976) carried out a study to investigate the correlation between the occurrence of pterygia and the 'dry eye', but were unable to demonstrate a significant difference between patients with pterygium and controls. This study fails to support the hypothesis of Mackie (1971) and Paton (1975), who suggest that there is a primary abnormality of the tear film which predisposes to pterygium formation.

Conclusions

Although there are some unexplained features, the overall epidemiological findings and the pathology of the lesions suggest that ultraviolet radiation is the major factor in the development of solar keratosis (pterygium) and, in consequence, the high incidence of squamous cell carcinoma of the conjunctiva in the tropics. Other cofactors, some of which have been discussed, may enhance the process. While latitude is the most important factor determining the exposure to ultraviolet light, many geographical factors such as cloud, altitude, and vegetation will influence the dose to the conjunctiva. Such factors may explain some of the variable frequencies in the tropics.

Our thanks are due to the Malawi Ministry of Health for permission to publish, Professor H. Spencer and Dr J. Borgstein, who initiated and maintained the histopathology service link between Malawi and St. Thomas's Hospital Medical School, the technicians in the Department of Morbid Anatomy for preparing the slides, Mr J. Fenton for help with photography, and Miss V. Gibson for secretarial help.

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Isolation of *Chlamydia trachomatis* from different areas of conjunctiva in relation to intensity of hyperendemic trachoma in school children in Southern Tunisia

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SUMMARY The simplified one-passage technique of culture in irradiated McCoy cells, in conjunction with certain other developments in technique, was used to isolate *Chlamydia trachomatis* from specimens collected from 78 children with trachoma in Douz, Southern Tunisia. The results show that *C. trachomatis* is not confined to the upper tarsal area of the conjunctiva in hyperendemic trachoma. The higher isolation rate and corresponding increase in the number of inclusions obtained from swabbings of the upper fornix and lower lid in addition to the conventional collection from the upper tarsus show the superiority of collecting specimens for culture from the whole conjunctiva. Specimens could be collected from the whole conjunctiva by using 1 swab for each eye and pooled for subsequent inoculation, so that the laboratory incurred no additional work. A close correlation was observed between isolation rate, together with the number of inclusions obtained in cell culture, and intensity of inflammatory disease in hyperendemic trachoma. The sensitivity and practicability of this cultural test should provide a valuable laboratory index for use in epidemiological and therapeutic studies of trachoma.

The simplified one-passage technique of culture in irradiated McCoy cells provides a rapid and sensitive test for the primary isolation of *Chlamydia trachomatis* (Darougar *et al.*, 1971). Conjunctival swabbings (Darougar and Jones, 1971) and transport of clinical specimens frozen in a cryoprotectant medium in a liquid nitrogen refrigerator (–180°C) (Darougar *et al.*, 1972) have further increased the sensitivity and practicability of the test. With this cultural technique chlamydial isolates were obtained in up to 90% of cases of chlamydial ocular infections in London (Darougar *et al.*, 1977), 68% of cases of non-specific urethritis (Alani *et al.*, 1977), and from the cervix of 90% of patients suffering from chlamydial ocular infections and mothers of babies with TRIC ophthalmia neonatorum (Darougar *et al.*, 1972).

The purpose of this study was to compare the isolation rate of *C. trachomatis* from specimens collected from the whole conjunctiva with the isolation rate from specimens collected from the upper tarsus alone (the conventional method), and to assess the relationship of the isolation rate to the severity of active hyperendemic trachoma.

Subjects and methods

Patients included in this study were selected from a group of children attending a primary school in Douz, Southern Tunisia, who were part of a long-term study of the natural history and the control of trachoma (Dawson *et al.*, 1974; Dawson *et al.*, 1976).

CLINICAL EXAMINATION

The clinical signs observed with a Haag-Streit slit-lamp in the cornea and conjunctiva were recorded on a proforma by means of an extension of the scoring system proposed for the study of trachoma (Dawson *et al.*, 1975). The signs were graded from 0 to 3, and the intensity of inflamma-

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tory disease of the upper tarsal conjunctiva and the whole conjunctiva was calculated by the method described elsewhere (Dawson *et al.*, 1975).

COLLECTION OF SPECIMENS

The conjunctiva of each eye was anaesthetised with 2 to 3 drops of Jocaine (cocaine HCl 4 g, adrenaline acid tartrate 0·15 g, sodium metabisulphite 0·1 g, neomycin sulphate 0·5 g, chlorhexidine acetate 0·1 % 5 ml, distilled water to 100 ml) (Darougar and Jones, 1971). Duplicate smears were taken from the upper tarsus of each eye for the detection of chlamydial inclusions by means of an indirect fluorescent antibody stain and Giemsa's stain. (The results of this study will be reported elsewhere.) After this conjunctival swabbings for the isolation of Chlamydia were collected from the upper tarsus of each eye. Separate swabbings were also collected from the upper fornix and lower lid conjunctiva of each eye. Paired swabs from the upper tarsus of the right and left eye were pooled in plastic capsules containing 2SP transport medium (Gordon *et al.*, 1969). Similarly, swabbings from the rest of the conjunctiva (upper fornix and lower lid) of both eyes were pooled. All conjunctival swabbings were stored immediately in a portable liquid nitrogen refrigerator (–180°C) for transport to the laboratory in London. Here they were stored in a refrigerator at –70°C for a period of 6 to 9 months until they were inoculated into cell cultures.

CELL CULTURE

The methods of culture in irradiated McCoy cells and the identification of inclusions are described elsewhere (Darougar *et al.*, 1971). The number of inclusions present in each coverslip at first passage was recorded.

Results

Seventy-eight children aged between 6 and 10 years with active trachoma were included in this study.

ISOLATION FROM DIFFERENT AREAS OF THE CONJUNCTIVA

Of 78 paired conjunctival specimens *C. trachomatis* was isolated from 23 (29%) from the upper tarsus and 29 (37%) from the rest of the conjunctiva (upper fornix and lower lids).

In culture the average ratio of the number of inclusions obtained from the upper tarsus to the number obtained from the whole conjunctiva was 1 to 14. Six cases were positive only in the upper fornix and lower lid, and in 4 of those the number of inclusions found was fewer than 7.

ISOLATION IN RELATION TO INTENSITY OF UPPER TARSAL CONJUNCTIVAL INFLAMMATION

The isolation rates and the numbers of inclusions obtained from the whole conjunctiva for various grades of intensity of inflammation are shown in Table 1. The highest isolation rate (82%) was obtained from cases of severe trachoma. The isolation rates from the upper tarsus in relation to McCallan's stages of trachoma are shown in Table 2.

Discussion

The simplicity, speed, and relatively non-traumatic nature of conjunctival swabbings used for this study confirms the previous report (Darougar and Jones, 1971) that swabbing is the method of choice for the collection of conjunctival specimens in field studies or for routine diagnostic laboratory work.

The results confirm the previous study (Darougar *et al.*, 1971) that *C. trachomatis* is not confined to the upper tarsal area of the conjunctiva in hyperendemic trachoma. Collecting specimens from the upper fornix and lower lid, in addition to the conventional collection from the upper tarsus, increases the isolation rate.

It may be argued that initial scrapings of the conjunctiva may reduce the isolation rate of chlamydia from subsequent swabbings. However, studies by Darougar *et al.* (1971) have shown that, despite there being less chlamydial agent in subsequent specimens and regardless of the order of collection by swabbing or scraping, the second specimens were as frequently positive as the first

Table 1 *Isolation of Chlamydia trachomatis in relation to the intensity of trachomatous inflammation in the whole conjunctiva*

Grade of severity	*No. of patients*	*No. of positives*	*Average no. of inclusions*
4–Severe	11	9 (82%)	774
3–Moderate	37	18 (49%)	115
2–Mild	27	2 (7%)	16
1–Trivial	3	0	0

Table 2 *Isolation of Chlamydia trachomatis in relation to McCallan's stages of trachoma in the upper tarsus*

Stages	*No. of patients*	*No. of positives*	*Average no. of inclusions*
I	9	2 (22%)	317
II	16	8 (50%)	754
III	53	19 (36%)	143

specimens. The higher isolation rate and corresponding increase in the number of inclusions obtained from the whole conjunctiva show the superiority of collecting specimens from the whole conjunctiva over the conventional collection from the upper tarsus area alone. In this study specimens were collected from various areas with separate swabs. In routine work specimens could be collected from the whole conjunctiva with the use of 1 swab for each eye. These swabs should be pooled in 1 capsule for subsequent inoculation, thereby incurring no additional workload in the laboratory.

The high isolation rate of 82% obtained in cases of severe trachoma and the close correlation between the grades of intensity of trachomatous inflammation and the isolation rate in irradiated McCoy cells demonstrate the sensitivity of this cultural test in field studies and show that the test could be used as a laboratory index of severity of hyperendemic trachoma.

The distribution of isolation from the upper tarsus in relation to McCallan's stages of trachoma indicates that this classification is not a good index of the presence of *C. trachomatis* and does not correlate with the severity of disease.

The high isolation rate in trachoma stage III indicates that there is continuing florid disease even in the presence of scarring. The progress from stage II to stage III can therefore not be regarded as improvement.

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Surgery for trachoma in Burma

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SUMMARY The problem of trachoma in Burma is presented. For its major sight-threatening complication of trichiasis a surgical procedure is described which is simple, effective, economical, and without any cosmetic blemish.

With this procedure 1861 cases of different grades of trichiasis were operated upon at the Eye, ENT Hospital, Rangoon, with 528 cases followed up at 1 year. The results are entirely satisfactory when the operations are performed for first and second degree trichiasis, and for trichiasis of our third degree grading the success rate is 95%.

Trachoma is prevalent in Burma and is known to have existed as early as AD 800–1200. It is a disease of the central dry zone, and the mere presence of trachomatous 'sleepy eye' is enough to identify the person as a native of that area. The incidence is high (Wilcocks, 1944, 1949), but no thorough study and survey of the disease was done until 1962.

In April 1962 a team of senior ophthalmologists (including the author) did a road-side survey of trachoma in 2 districts of the dry zone. This indicated that trachoma was present in more than 80% of 3862 persons examined and confirmed that it was the single most important cause of blindness in the region. A trachoma control project was first launched by the national health authorities in 1964. Since 1966 the project has been assisted by WHO and UNICEF.

The overall cost for the programme to the end of March 1974 from its beginning in 1964 has been £600 000, and approximately 70 000 cases of loss of vision have been prevented (Ko Lay *et al.*, 1976).

During the natural course of the disease the palpebral conjunctiva is severely scarred owing to the replacement of trachoma follicles by fibrous tissue. The tarsal plates, which in the initial phase show a cellular infiltration are later deformed and thickened. These 2 mechanisms lead to entropion and/or trichiasis.

There are 4 main divisions of the work of the campaign: (1) Finding and registering the trachoma patients; (2) treatment of the disease itself; (3) treatment of the complications, for example surgical repair for trichiasis; (4) health education. This paper is concerned with the third of these.

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Materials and methods

Between January 1971 and December 1975, 1861 patients from different parts of Burma were referred and operated upon at the Eye, ENT Hospital, Rangoon.

Trichiasis cases were classified by the author into 3 grades: (1) Trichiasis involving half the length of lid margin, the lid being soft and pliable (459 patients); (2) trichiasis involving the whole length of lid margin, the lid being still soft and pliable (1008 patients); (3) trichiasis involving the whole length of lid margin, but the lid being hard on palpation. Pliability is lost and the eversion of eyelids becomes very difficult. The tarsoconjunctival margin becomes rounded off and there is general contraction of the conjunctival sac (394 patients).

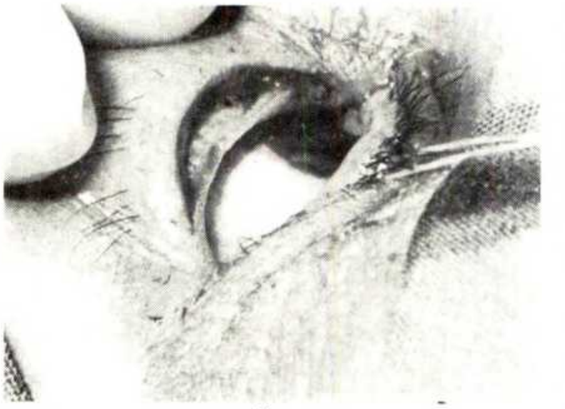
OPERATION FOR TRICHIASIS: THE GREY LINE SPLIT

The principle of this procedure is the eversion of the lid margin so that the cilia do not come in contact with the globe. The instruments required are 1 Bard Parker No. 15 knife and holder, 1 lid guard, 3 or 4 double-armed 5–0 black silk sutures, a petroleum jelly gauze roll for each eyelid, 30 × 5 mm.

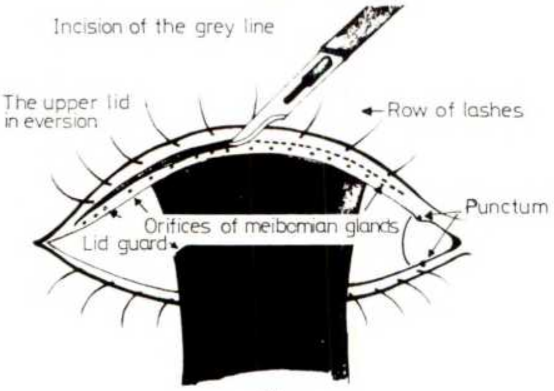
Local anaesthesia is provided by infiltration of 2 ml of 2% lignocaine into the neuromuscular plane of the upper eyelid, supplemented with topical surface anaesthesia of amethocaine (tetracaine) 1% into the conjunctival sac is sufficient for this procedure.

Important steps in the operation are: (1) Precise incision of the grey line; (2) accurate insertion of the sutures; (3) proper positioning of the gauze roll and tying of the sutures.

The incision. The free border is split into skin



1a



Incision of the grey line
The upper lid in eversion
Row of lashes
Punctum
Orifices of meibomian glands
Lid guard

1b

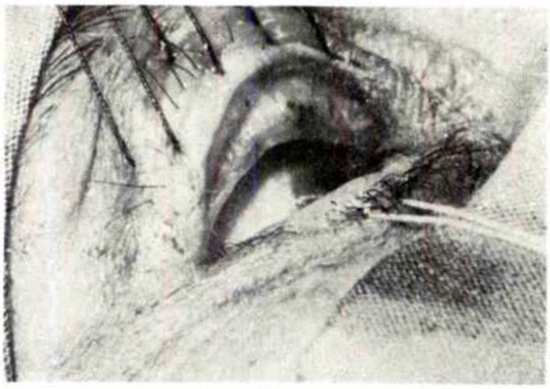
Figs. 1a and b *The lid margin is split into skin muscle and tarsoconjunctival layers*

muscle and tarsoconjunctival layers (Figs. 1*a* and 1*b*). The dissection is carried upward carefully and precisely for 2 or 3 mm to obtain good separation. The depth of the incision is of critical importance, because too superficial an incision fails to achieve the desired amount of elevation of the lashes, while an unnecessarily deep incision causes haemorrhage, formation of excess granulation tissues, and cosmetic blemish.

The sutures. One arm of a double-armed suture is passed through the conjunctiva of the upper fornix just above the tarsal plate, emerging on the skin surface at a point 6 mm from the margin of the lid. The second suture enters the conjunctiva in close proximity to the first one, but the needle is then passed anteriorly to the tarsal plate to emerge on the skin surface at a point 1 mm from the lid margin. Usually 3 sutures are placed equidistant from one another (Figs. 2*a* and 2*b*).

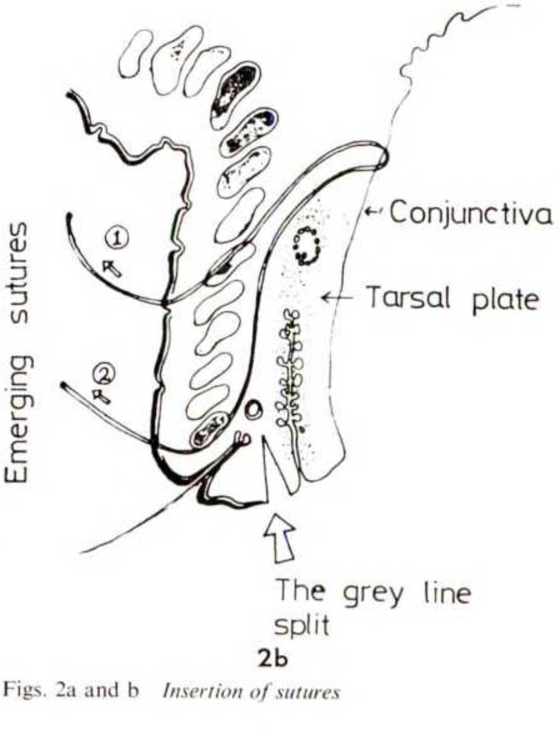
Positioning of gauze roll. A petroleum jelly gauze roll impregnated with antibiotic solution is placed horizontally between the 2 arms of the sutures and properly tied (Figs. 3*a*, 3*b*, 3*c*). The gauze roll acts as a fulcrum for the everting force of the sutures. Tightening of the sutures causes the grey line incision to gape and everts the lid margin with the lashes. This procedure elevates the lashes by approximately 90°, the amount depending on the pliability of the lid.

The grey line wound is allowed to heal by grannulation tissue, which gradually becomes covered with



2a

After insertion of the sutures



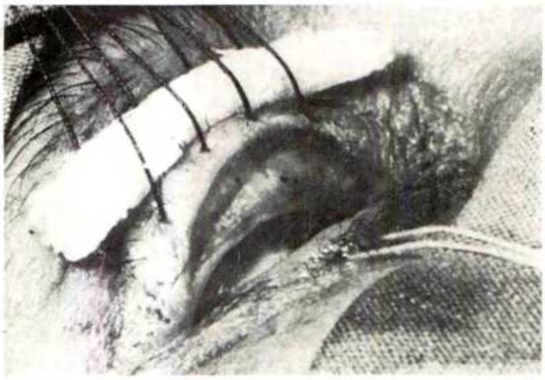
2b

Figs. 2a and b *Insertion of sutures*

epithelium. The stitches are removed after 2 weeks (Figs. 4*a* and 4*b*).

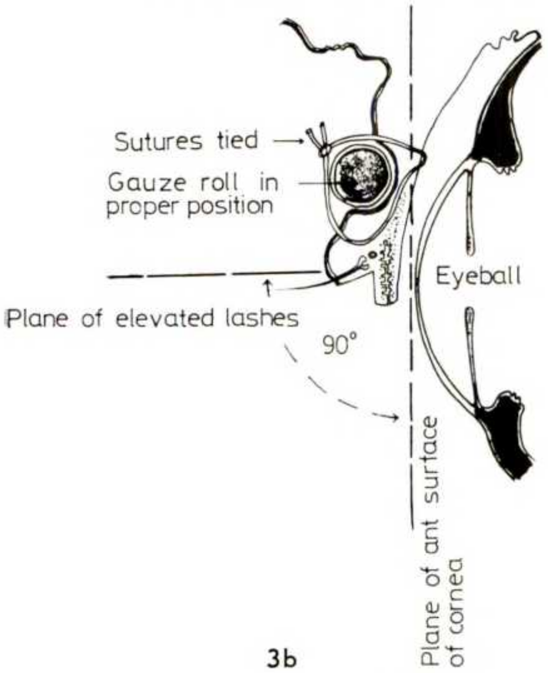
Results

Of the 1861 trichiasis cases operated upon between January 1971 and December 1975 only 528 were available for follow-up 1 year after operation

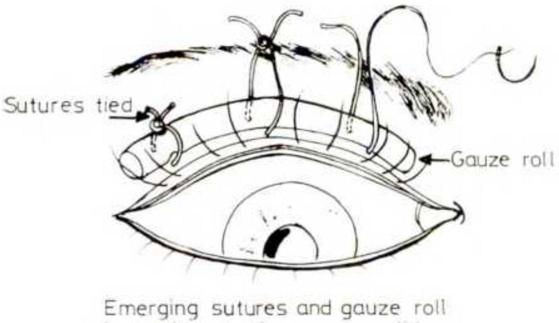


3a

Lid and eyeball in sagittal section

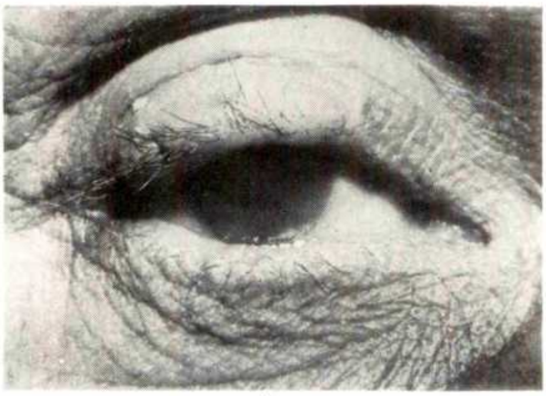


3b



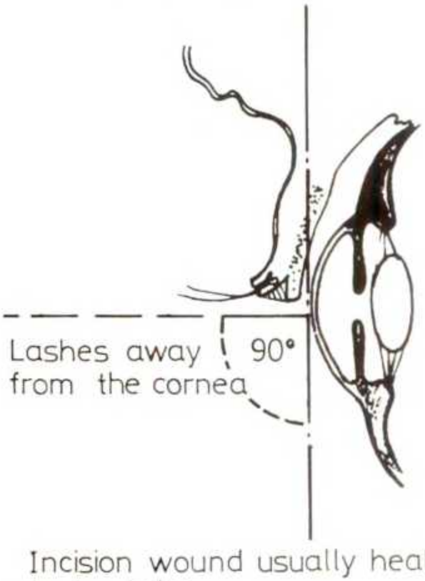
Emerging sutures and gauze roll in position on the upper eye lid

3c



4a

After operation



Incision wound usually healed after two weeks

4b

Figs. 4a and b *Postoperative result, showing the eversion of the eye lashes*

← Figs. 3a, b, and c *Positioning of gauze roll*

Table 1 *Successful operations by the grey line split*

Degree of trichiasis	*Number of patients*	*Number successful at 1 year*
1	128	128
2	272	271
3	128	121

(Table 1). Of these 128 were grade I and all had a successful result. Out of 272 of our grade II, 1 case was observed to be a failure after 3 months. The lashes did not evert on the temporal half, though the degree of eversion was better than immediately after the operation. Of the remaining 128 cases categorised as our grade III, 121 were successful, but the remaining 7 cases had redeveloped trichiasis as early as 1 month postoperatively. The remaining 1333 cases never returned for assessment and recording after removal of their stitches at the end of the second week.

The degree of eversion achieved tended to be 90° or less in grade III patients, where the conjunctiva and tarsal plate were very severely scarred. Failure was more frequent within this group. The permanency of the result of this operation also depends on the state of trachoma. If there are recurrences of infection with repeated scarring of the conjunctiva and tarsus the results are usually unsatisfactory. It is therefore advisable to continue medical treatment of trachoma along with the surgery or to carry out surgery when the disease is quiet.

Discussion

The superiority of this method over other surgical techniques lies on two main points: (1) *Simplicity*, for no assistant is needed and the procedure takes only 5 to 10 minutes. (2) *The depth of incision* may be varied with the degree and state of trichiasis and/or entropion. Bleeding is minimal. Only a few instruments are required, as they can be sterilised wherever the operation is to be done. This is especially important when it is desirable for the doctor to go to the patient and more so when there are thousands of patients with trichiasis waiting for surgery all over the country.

Varying the depth of the incision to the degree and state of trichiasis is important. If the incision is too shallow, that is, less than 2 mm in depth, the lashes invert again after a few months because the cleavage is thin and it cannot effectively overcome the distorted tarsus. Only when the incision is deep enough, 2 to 3 mm, will it produce a widely separated postoperative intermarginal wound resulting in the desired eversion of eye lashes.

Economy of the operation must also be stressed. In Burma the cost of materials for surgery is approximately equal to 5p. The outpatient surgery and minimal postoperative care mean negligible loss of working time for patients.

Paramedical personnel such as health assistants and nurses can be trained to master this surgical technique in a short time. In a country like Burma where the prevalence of trichiasis is between 5 and 7% in the trachoma endemic area, and where there are few ophthalmologists, this fact is important.

I acknowledge the help I received from Professor G. W. Crock, Dr Hector Maclean, and Dr Peter Henderson in preparing this paper. Miss Jane O'Donnell typed the manuscript, and Mrs Glenys Van Den Brenk and Miss Maree Bradbury prepared the photographic material.

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British Journal of Ophthalmology, 1979, **63**, 117–119

Surgical correction of senile entropion of the lower lid with fascia lata sling

S. N. M. RIZK AND A. K. MISHRA
From the Nottingham Eye Hospital

SUMMARY A method of surgical correction of senile entropion of the lower lid with heterogenous fascia lata sling is described with no tissue loss and minimum of surgical trauma.

Numerous surgical techniques described in the past for correction of senile entropion of the lower lid indicate that there is no reliable single method to deal with the problem. The object of this paper is to describe a surgical technique using a heterogenous fascia lata sling for the correction of senile entropion.

Surgical pathology

Jones (1960) has described the following changes in the senile eye: *(a)* The senile absorption of orbital fat causes some degree of enophthalmos, which reduces the pressure of the globe against tarsi. *(b)* The skin and superficial fascia become atonic, redundant, and less adherent to underlying pre-septal muscle. *(c)* The lower preseptal muscle becomes less fixed to the underlying septum orbitale and loses its pressure against the base of the tarsus and moves upwards over the pretarsal during contractions of the muscle (Fig. 1). *(d)* The deep fascial layers attached to the base of the tarsus become relaxed not only by the enophthalmos but also by the usual atony accompanying the ageing process. These factors reduce the pressure against the lower border of the tarsus and increase it against the upper border, allowing the tarsus to turn in at a right-angle (Fig. 2).

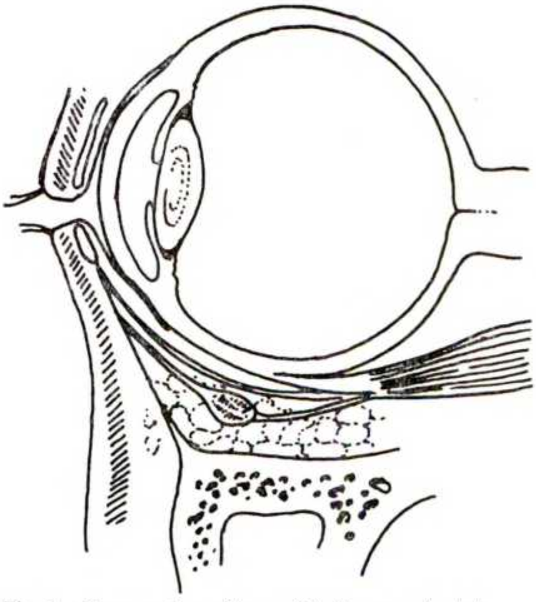

Fig. 1 *Cross-section of lower lid of a normal adult*

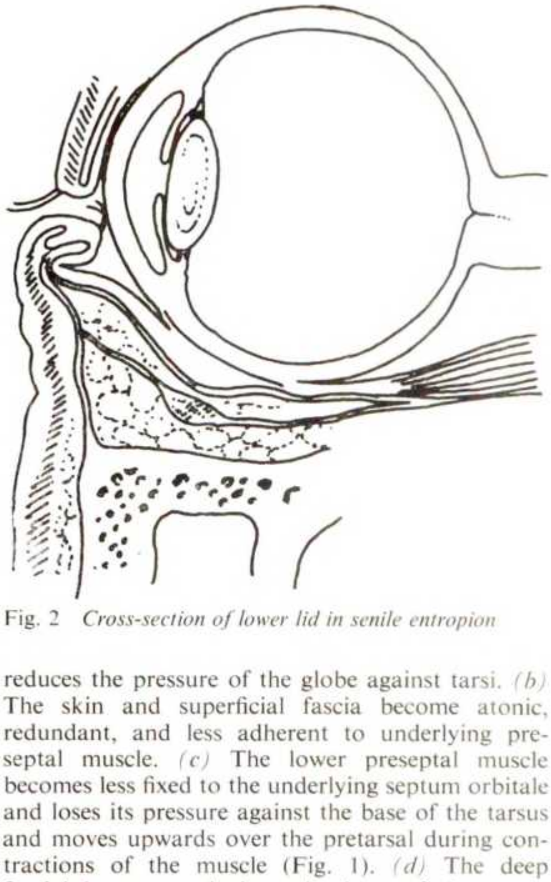

Fig. 2 *Cross-section of lower lid in senile entropion*

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Operative technique

The skin of the lower lid is cleaned with 1% chlorhexidine solution. It is then infiltrated with about 2 ml of 1% lignocaine—adrenaline (1 100 000) along its entire length from the medial canthus to just outside the lateral orbital margin. The injection is given subcutaneously.

Two vertical incisions about 5 mm long are made, one over the medial canthal tendon about 3 to 4 mm from the medial canthus and the other over the outer orbital rim level with the outer canthus. The subcutaneous tissue is dissected with sharp-pointed scissors to expose the medial canthal tendon, and the same procedure is carried out at the outer orbital rim to expose the periosteum. A sharp-pointed aneurysm needle is introduced through the lateral incision and directed medially level with the lower half of the lower tarsal plate, its tip being constantly felt with the fingers until its eye comes out through the medial incision. If the bridge of the nose is not very prominent it is sometimes easier to pass the needle from the medial to the lateral side (Fig. 3).

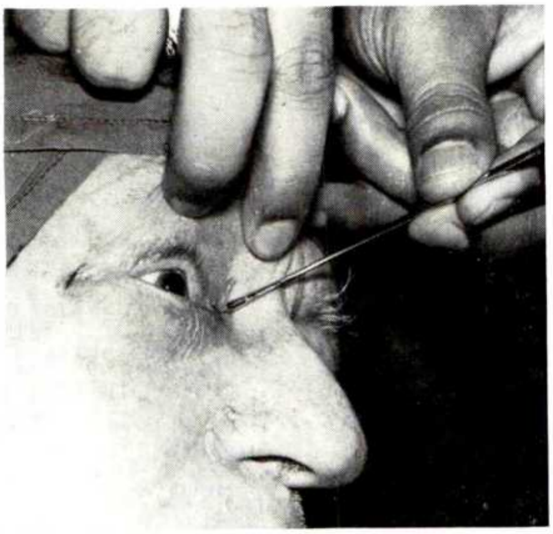

Fig. 3 *The aneurysm needle in the lower lid*

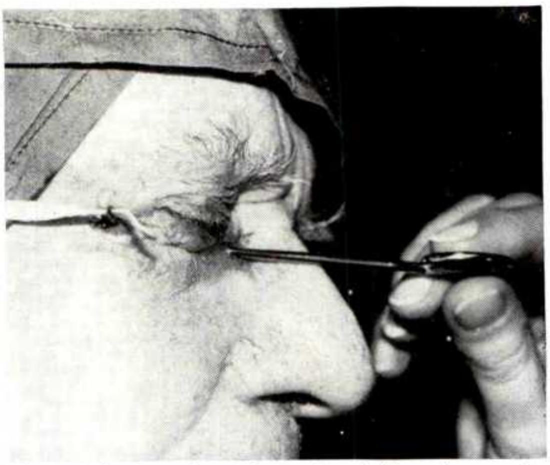

Fig. 4 *The fascia lata is being threaded into the eye of the aneurysm needle*

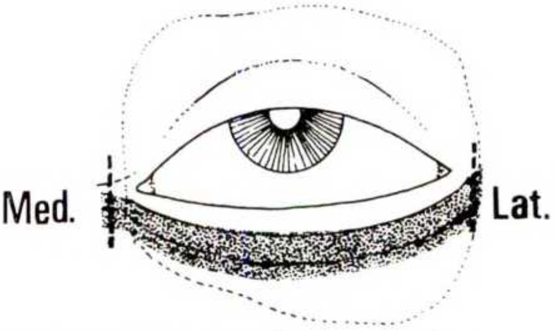

Fig. 5 *The eye with fascia lata sling in position*

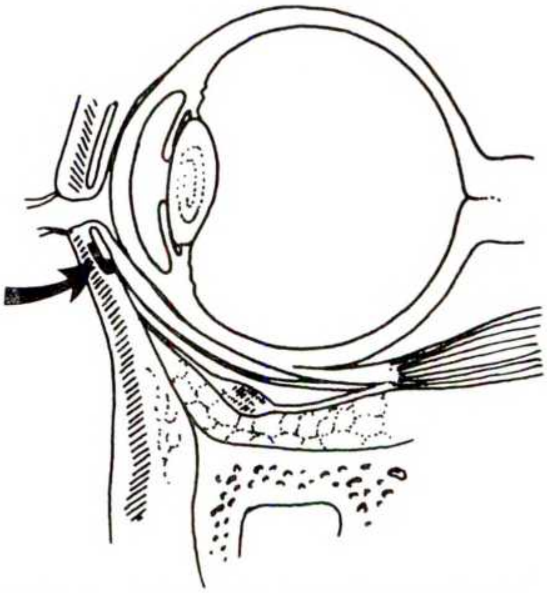

Fig. 6 *Cross-section of the eye with fascia lata sling in position*

A strip of heterogenous fascia lata (derived from oxen) cut about 3 mm wide and 10 cm long and washed in saline solution is threaded through the aneurysm needle, which is withdrawn, taking the strip with it (Fig. 4). One end of the strip is stitched to the medial canthal tendon with 5–0 Dexon sutures. The strip is now made slightly taut, the right tension being judged by the appearance of a depression in the skin overlying the strip of fascia lata. The lateral end of the strip is now firmly stitched to the periosteum covering the outer orbital rim. The excess of strip is cut off and buried under the orbicularis. The wounds are then sutured in layers.

Results

This surgical procedure has so far been carried out on 62 cases. One phthisical eye is included in the series. The follow-up period varied from 6 weeks to 2 years. Apart from 2 cases, in which the entropion recurred 6 weeks after surgery, the results were very encouraging. The same procedure was repeated on the 2 patients with recurrence, with a satisfactory result. Most of the cases have been followed up for over 2 years now without any recurrences. None of these patients showed any obvious scar or cosmetic problem. None had any infection or postoperative rejection.

Discussion

In this technique there is no tissue loss and very little surgical trauma. The fascia lata strap supports the lower part of the tarsal plate (Fig. 5) and orbital septum and holds it near the globe (Fig. 6). Transfixing the orbicularis fibres by tunnelling the strip through them may enhance the effectiveness of the operation by preventing the muscle from advancing upward on the tarsal plate. Injury to important structures is easily avoided, and there is good haemostasis. Use of Dexon sutures avoids the need to remove them at a later date.

A similar procedure has been described by Ray A. Elliott, Jr. (1962), who used autogenous fascia lata. He reported 6 cases, and results were 100% satisfactory.

Fascia Lata is a sterile preparation marketed by Ethicon.

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British Journal of Ophthalmology, 1979, **63**, 120–124

The contralateral upper eyelid in ptosis: some observations pertinent to ptosis corrective surgery

H. K. MEHTA
From the Eye and Cottage Hospital, Caernarvon, Gwynedd, Wales

SUMMARY The validity of Hering's law in corrective surgery for ptosis is demonstrated for the first time. It is also shown how Hering's law has been utilised in corrective surgery for unilateral ptosis to elicit a predominant response from the unoperated contralateral upper eyelid. Other implications of reciprocal innervation of the 2 upper eyelids are discussed and a tentative hypothesis is postulated that in a case of true unilateral levator ptosis the fellow upper eyelid will show compensatory retraction.

Compensatory retraction of the contralateral upper eyelid is a relatively common occurrence in patients with unilateral ptosis of an upper eyelid. But the phenomenon has received scant attention in ophthalmic literature. Evidence is presented here to show that as well as occurring frequently in ptosis this phenomenon also occurs in mechanical ptosis, and that it has the following clinical implications.

Firstly, in some patients this compensatory retraction of the fellow upper eyelid constitutes as much a cosmetic blemish as does the ptosis in the primarily affected eye.

Secondly, just as surgical operation on the extraocular muscles of one eye has effects on the actions of the corresponding muscles of the fellow eye (a phenomenon repeatedly exploited in the surgical management of patients with strabismus), so does a similar phenomenon operate in corrective surgery for ptosis. It can be utilised to 'balance' the position of the 2 upper eyelids, as follows: (*a*) The improvement of unilateral ptosis by levator resection is frequently accompanied by reduction in the compensatory retraction of the unoperated fellow upper eyelid. (*b*) In some patients in whom gross surgical overcorrection of unilateral ptosis has caused unsightly ipsilateral upper eyelid retraction the unoperated contralateral upper eyelid develops a compensatory ptosis. When the overcorrection is relieved by levator recession surgery, the compensatory ptosis of the contralateral upper eyelid is also relieved.

Thirdly, in cases of bilateral ptosis, when unilateral surgical correction is carried out the improvement of the ptosis of the operated eyelid may accompany worsening of the ptosis of the untreated upper eyelid.

To my knowledge this is the first report of clinical utilisation of this synkinetic oculopalpebral phenomenon in ptosis corrective surgery.

Case reports

These have been classified into 4 categories. Group I: Unilateral ptosis with mild to moderate compensatory retraction of the contralateral upper eyelid (Case 1). Group II: Unilateral ptosis with gross compensatory retraction of the contralateral upper eyelid (Cases 2 and 3). Group III: Bilateral ptosis (Cases 4 and 5). Group IV: Unilateral mechanical ptosis with compensatory retraction of the contralateral upper eyelid (Cases 6 and 7).

CASE 1

A woman aged 74 with senile ptosis of the left upper eyelid and a mild compensatory retraction of the right upper eyelid (Fig 1*a*). Ptosis correction of the left upper eyelid was carried out by a 10-mm levator resection and a 2-mm tarsectomy. The result 8 weeks later shows a satisfactory correction of the ptosis and diminution of the retraction of the unoperated right upper eyelid (Fig. 1*b*).

CASE 2

A girl aged 13 with congenital ptosis of the left upper eyelid and total inaction of the ipsilateral superior rectus also had gross compensatory retraction of the right upper eyelid (Fig. 2*a*). The parents

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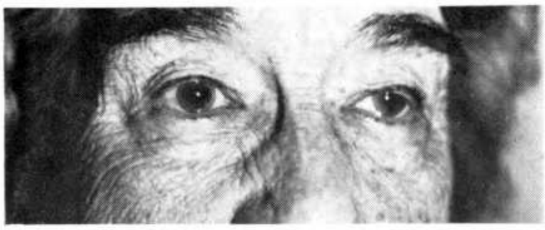

Fig. 1 (a) *Preoperative appearance of senile myogenic ptosis of left upper eyelid and mild compensatory retraction of the right upper eyelid*

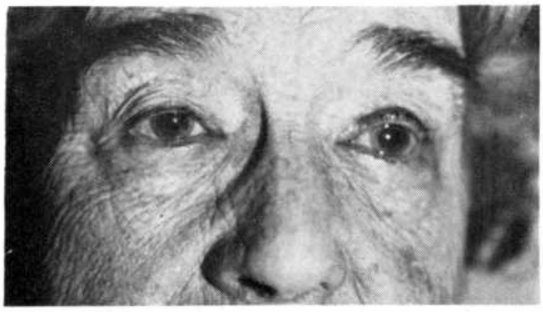

Fig. 1 (b) *Postoperative appearance 2 months after a left levator resesection of 10 mm, and 2 mm tarsectomy performed under local anaesthesia as a day case: satisfactory correction of the ptosis and diminution of the retraction of the unoperated right upper eyelid*

and the child were as much concerned about the staring right eye as they were about the ptosis. As there was total absence of Bell's phenomenon, and as the left eye used to remain half open during sleep, when discussing surgical correction it was explained to the parents that full correction of the ptosis might usher in exposure keratopathy, and that a small levator resection of the left upper eyelid would probably not only produce some improvement in the ptosis but also that the right upper eyelid would probably respond by lessening its retraction. The result of a deliberately small levator resection (10 mm) of the left upper eyelid is shown in Fig. 2*b*.

The improved appearance in this case has been achieved by 3 factors—minimal improvement in the ptosis, formation of a lid fold, and a reduction in the retraction of the right upper eyelid.

CASE 3

A man aged 82 when seen in February 1976 had ptosis of the left upper eyelid due to a total left 3rd nerve palsy. He also had gross compensatory retraction of the right upper eyelid (Fig. 3*a*). Six months later, there being no improvement in the 3rd nerve palsy, a 14-mm resection of left levator with 2-mm tarsectomy was carried out. The primary aim was to reduce the compensatory retraction of the right upper eyelid, as it was accepted that the paralytic ptosis was unlikely to improve even after the ipsilateral levator resection. The result 3 months after surgery (Fig. 3*b*) shows the expected reduction of the retraction of the right upper eyelid.

CASE 4

A woman aged 54 with severe bilateral acquired ptosis of undetermined aetiology wanted surgical correction because the drooping eyelids severely obstructed her vision (Fig. 4*a*). One week after a left levator resection of 14 mm and 2 mm tarsectomy there was an improvement of ipsilateral ptosis, but worsening of the ptosis of the right upper eyelid (Fig. 4*b*). The final satisfactory result after right levator resection is seen in Fig. 4*c*.

The worsening of the ptosis of the unoperated

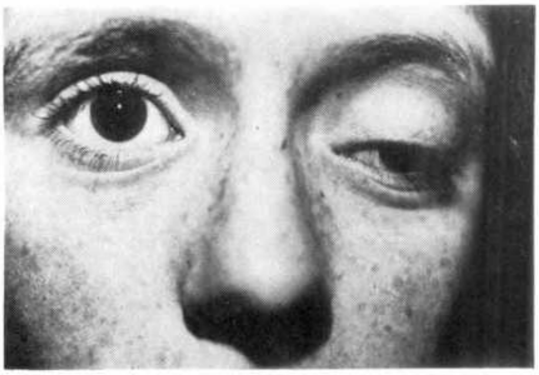

Fig. 2 (a) *Preoperative appearance of congenital ptosis of the left upper eyelid and gross compensatory retraction of the right eyelid in a child aged 13*

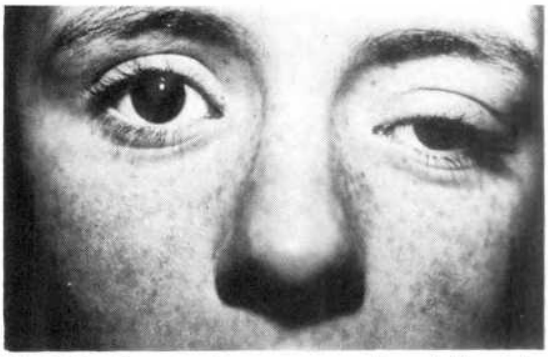

Fig. 2 (b) *Postoperative appearance after a deliberately small resection of 10 mm of the left levator shows reduction of ptosis and formation of a lid fold on the left upper eyelid, and the anticipated reduction of retraction of the right upper eyelid*

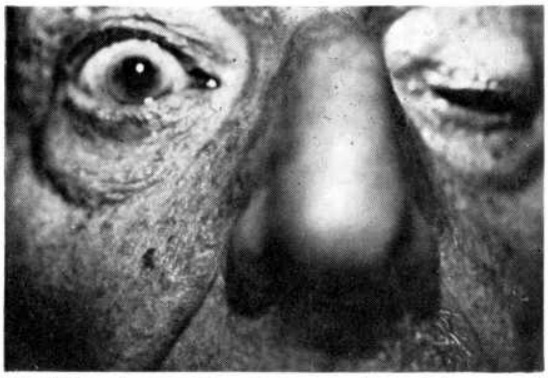

Fig. 3 (a) *Preoperative appearance of paralytic ptosis of the left upper eyelid due to a total left 3rd nerve palsy of 6 months' duration. Note the gross compensatory retraction of the right upper eyelid*

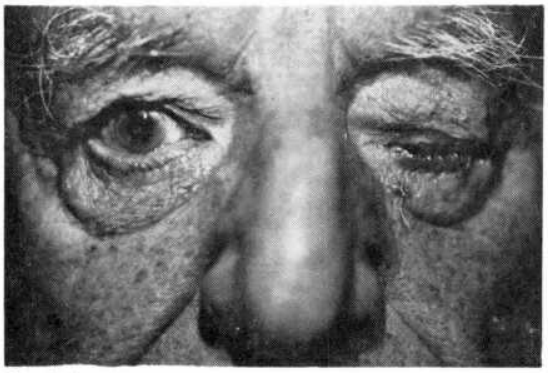

Fig. 3 (b) *Postoperative appearance after 14 mm resection of levator and 2 mm tarsectomy on the left side with a primary view to eliciting reduction of retraction of the right upper eyelid*

upper eyelid after contralateral levator resection is noteworthy.

CASE 5

A 76-year-old man with senile myogenic ptosis of the left upper eyelid did not have a compensatory retraction of the right eyelid (Fig. 5*a*). Phenylephrine 10% drops were instilled in the left eye only. Ten minutes later there was improvement in the ptosis of the left eye and reciprocal drooping of the upper eyelid of the right eye (Fig. 5*b*).

The absence of compensatory retraction of the right upper eyelid suggests that possibly this may eventually turn out to be a case of bilateral ptosis.

CASE 6

A 60-year-old man was operated on for repair of a laceration of the left upper eyelid which also involved the lateral half of the levator palpebrae. Fig. 6 shows the appearance 2 weeks after the repair. Note the mechanical ptosis of the left upper eyelid and retraction of the right upper eyelid.

CASE 7

A man aged 73 with herpetic keratitis developed 'mechanical ptosis' of the right upper eyelid and

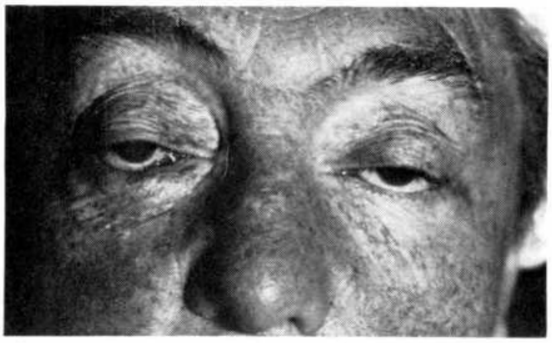

Fig. 4 (a) *Severe bilateral acquired ptosis of unknown aetiology in a woman aged 54—preoperative*

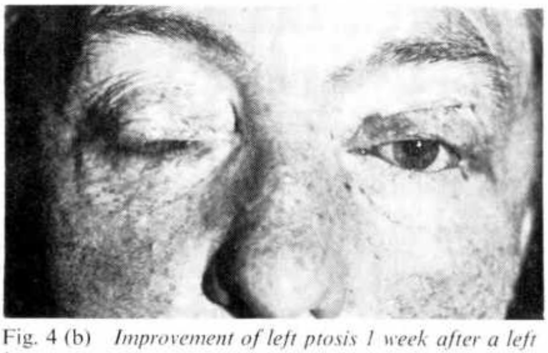

Fig. 4 (b) *Improvement of left ptosis 1 week after a left levator resection of 14 mm and 2 mm tarsectomy. Note the worsening of ptosis of the right upper eyelid*

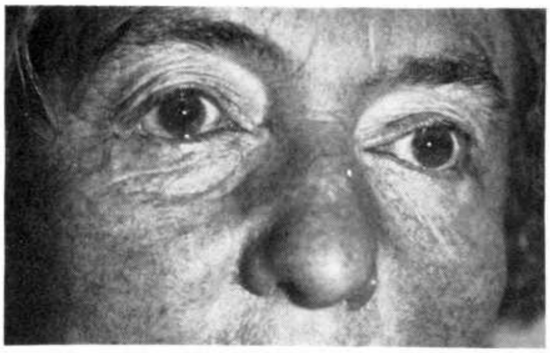

Fig. 4 (c) *Final satisfactory appearance after right levator resection* compensatory retraction of the left upper eyelid (Fig. 7).

Discussion

Compensatory retraction of the contralateral upper eyelid in cases of unilateral ptosis was first reported by Walsh (1957) and subsequently by Lewallen (1958), Jain (1963), Gupta *et al.* (1964), and Gay *et al.* (1967). They all explained the reciprocity of the levators of the 2 upper eyelids on the basis of a reflex mechanism obeying Hering's law. Kennard and Smyth (1963) demonstrated the presence of stretch receptors in the levator muscles. However, so far there have been no reports of clinical utilisation of Hering's law in corrective surgery for ptosis. Other authors (Table 1), with the exception of Beard (1976), who have reported the results of surgical correction of unilateral ptosis appear to have ignored (by letting pass unremarked) the compensatory posture alteration of the unoperated contralateral upper eyelid despite the fact that in some instances this compensatory response has contributed much to improve the patient's appearance. Similarly, some authors (Mustardé, 1968; Mustardé *et al.*, 1970) studying the effects of instillation of cocaine-adrenaline or guanethidine drops unilaterally into the eye having ptosis have restricted their observations only to the eye under study. However, the photographs in their communication clearly indicate posture alteration of the fellow upper eyelid.

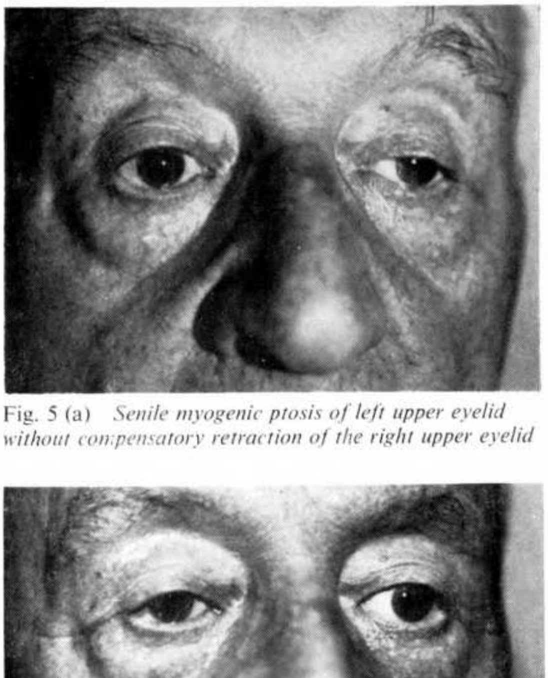

Fig. 5 (a) *Senile myogenic ptosis of left upper eyelid without compensatory retraction of the right upper eyelid*

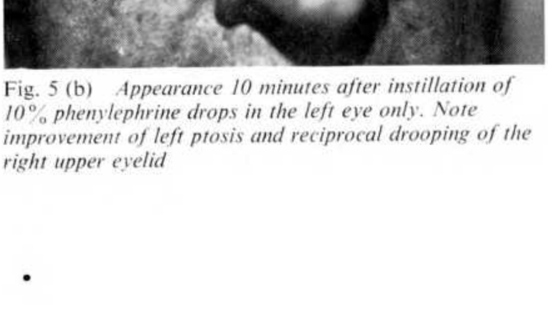

Fig. 5 (b) *Appearance 10 minutes after instillation of 10% phenylephrine drops in the left eye only. Note improvement of left ptosis and reciprocal drooping of the right upper eyelid*

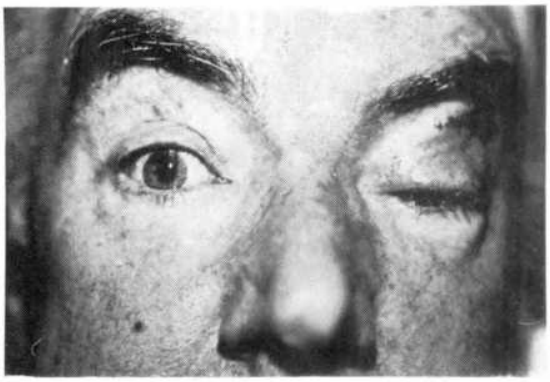

Fig. 6 *Mechanical ptosis of left upper eyelid 2 weeks after repair of a laceration involving the levator. Note the compensatory retraction of the right upper eyelid*

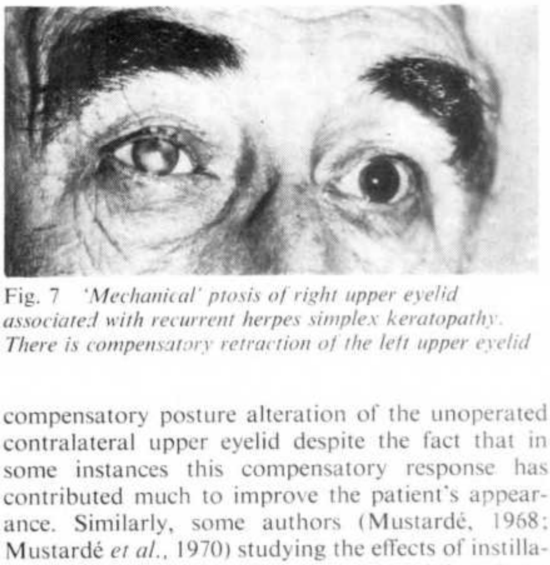

Fig. 7 *'Mechanical' ptosis of right upper eyelid associated with recurrent herpes simplex keratopathy. There is compensatory retraction of the left upper eyelid*

It can be seen from my Cases 2 and 3 of ptosis of poor prognosis that I have utilised Hering's law predominantly to elicit a response from the unoperated contralateral upper eyelid. In my series of unilateral ptosis with contralateral upper eyelid retraction I have opted to perform resection of the levator of the eyelid showing ptosis. But if the validity of Hering's law is to be established for the corrective surgery of ptosis, then, theoretically at least, similar results should be expected to be obtained whether one resected the levator of the

Table 1 *References from significant contributions to the literature on ptosis wherein improvement of* unilateral *ptosis after corrective surgery is reported without any remark about the obvious improved cosmesis brought about also by the reciprocal alteration in the postion of the unoperated fellow upper eylid*

Author	*Source*	*Page numbers*	*Figure numbers*
Beard, C. (1969)	*Ptosis*, 1st edn. Mosby: St. Louis	93, 94, 98, 101, 103, 216, 217, 221	7:16; 7:18; 7:23; 7:27; 7:28; 13:8; 13:9; 13:13
Callahan, A. (1966)	*Reconstructive Surgery of the Eyelids and Ocular Adnexa.* 1st edn. Aesculapius: Birmingham, Alabama	72; 98	72–73; 96–97
Fox, S. (1976)	*Ophthalmic Plastic Surgery*. 5th edn. Grune & Stratton: New York	374; 411	16–7 (I–J); 16–17 (A and B)
Mustardé, J. C., Jones, L. T., and Callahan, A. (1970)	*Ophthalmic Plastic Surgery Up-to-Date.* Aesculapius: Birmingham, Alabama	54, 55, 58, 59	63A, C; 64A, B; 68A, B; 69A, B
Rycroft, B. W. (1957)	*Transactions of the Ophthalmological Society of the United Kingdom*, 77, 501–511	507	158

ptosed eyelid or recessed the levator of the retracted eyelid. Evidence for the efficacy of the latter can be judged by the case of Maris reported by Reeh *et al.* (1976). This patient, like my Case 1, showed unilateral ptosis with retraction of the fellow upper eyelid. Maris considered the 'hyperelevation' to be the primary congenital defect in his case and therefore carried out recession of the ipsilateral levator. The postoperative photograph clearly shows compensatory elevation of the contralateral eyelid, which had ptosis. It therefore looks certain that Hering's law can be used effectively to balance 2 asymmetrically positioned upper eyelids. An obvious and logical corollary of this is in cases of bilateral ptosis, when unilateral corrective surgery for ptosis is carried out. The improvement of ipsilateral ptosis may be accompanied by worsening of the ptosis of the fellow upper eyelid. The patient can be warned about this.

An analysis of my own 20 cases of unilateral ptosis of varied aetiology has shown the presence of compensatory retraction in 19. (The only patient not showing compensatory retraction was Case 5 of this communication.) This leads me to postulate a tentative hypothesis that, if in a case of apparently unilateral levator ptosis there is absence of retraction of the fellow upper eyelid, one is probably not dealing with a true unilateral ptosis but with a potentially bilateral ptosis.

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Reeh, M. J., Beyer, C. K., and Shannon, G. M. (1976). *Practical Ophthalmic Plastic and Reconstructive Surgery*, 1st edn., p. 78 (Fig. 7–4). Lea & Febiger: Philadelphia.

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British Journal of Ophthalmology, 1979, **63**, 125–128

A new method of full thickness skin graft fixation

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SUMMARY A technique of free full thickness skin graft fixation utilising central and paracentral sutures between the graft and the depths of the recipient bed is described. The intrinsic fixation provided by these sutures allows larger free grafts, thus eliminating the need to use local flaps. These sutures also allow double free grafts—mucosal and dermal—for full thickness lower eyelid reconstructions. Patients do not need hospital admission and can resume normal activity immediately after the operation. One hundred and nine skin grafts secured by this technique have yielded very satisfactory results.

All methods currently employed to secure a full thickness skin graft to the recipient bed utilise the technique of the tie-over bolus. A firm pressure bandage is usually applied for the first few days to reinforce the stability of the graft. To ensure that the graft is not lifted off its bed by formation of haematoma under it, such patients are usually admitted to hospital so that their activity after the operation can be restricted for about a week. The aim of this communication is to describe and evaluate a new technique which in addition to the usual marginal sutures utilises central and paracentral sutures (in principle similar to the standard surgical practice of 'quilting' of large split-skin grafts in concave areas) to transfix full thickness skin grafts in oculoplastic surgery.

Patients and methods

One hundred and nine consecutive and unselected patients treated in my unit for oculoplasty with full thickness skin grafts between January 1973 and June 1977 have been included in this study. The size of the skin grafts varied between 1·2 and 3·5 cm in the longest diameter. The follow-up period ranged from 6 months to 4½ years.

Eighty-seven cases were treated for malignant or suspected malignant tumours; 14 of these in addition to a free skin graft needed a mucosal graft for full thickness lower eyelid reconstruction; 15 cases were treated for correction of lower eyelid ectropion, and 7 cases for xanthelasma All grafts were secured by 5–0 polyglycolic acid sutures (Dexon) by a technique briefly outlined previously (Mehta, 1977) and fully described here. The surgery was carried out under local anaesthesia as day cases except for 5 patients who were admitted to the hospital for social reasons. Tie-over bolus was not used in any of these 109 patients.

In the past 12 months the firm pressure bandage dressing has not been used in 14 grafts that were so situated as to be able to be covered by a cartella shield without the edge of the shield pressing on any part of the graft. To soak up any oozing blood eye pads were used on the *superficial* aspect of the shield, which was kept *in situ* with a bandage till the first dressing 48 hours later. Two of these 14 patients had ectropion of the lower eyelid of their only functional eye. These 2 patients were also treated as day cases. A large central hole was made in a cartella shield, which was the sole 'dressing' for these 2 skin grafts. The shield was kept *in situ* till the removal of central and marginal sutures on the 7th postoperative day.

All patients were given 2 co-trimoxazole tablets twice daily for 5 days. They were called to the hospital for the first dressing 48 hours after the operation, and were next seen on the 7th or 9th postoperative day for removal of all sutures. The subsequent clinic visits were at progressively doubled intervals till an annual follow-up period was obtained. They are then seen annually.

SURGICAL TECHNIQUE

Full thickness skin graft is obtained from the retroauricular sulcus or from the inner arm—allowance must be made for shrinkage of the graft. Subcutaneous fat of the graft is snipped off with scissors. The graft is now placed into the prepared recipient bed. One long edge of the graft is sutured with

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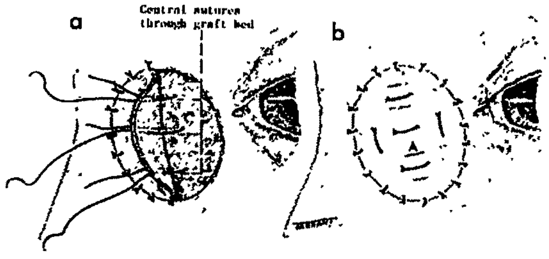

Fig. 1 *Author's technique of full-thickness skin graft fixation using marginal and 'central' sutures of 5–0 polyglycolic acid (Dexon). Reproduced from Mehta (1977)*

interrupted marginal sutures of 5–0 polyglycolic acid (Dexon) placed 2 or 3 mm apart. Central and paracentral sutures of 5–0 Dexon are now passed between the graft and the depth of the recipient bed (Fig. 1*a*). At least 4 such sutures are passed. For a large graft many additional sutures in 2 or more circles concentric with the graft edge are required. These 'central' sutures are not tied until after the remaining marginal sutures have been introduced and tied. The 'central' sutures are now tied under moderate tension to allow and maintain proper approximation between the graft and the recipient bed (Fig. 1*b*). A tie-over bolus is not necessary. A firm pressure dressing bandage is also not absolutely necessary.

Results

There was a 100% 'take' of the graft in all 109 patients. The usual transition of the colour of the graft from blotchy blue to healthy pink was observed in all cases between the 3rd and the 8th postoperative day. In one case of an 86-year-old woman (Fig. 2), there is a poor colour match of the graft obtained from the inner arm. She needed full thickness reconstruction of over three-quarters of the lower eyelid. The repair was carried out with free buccal mucosal and simultaneous free skin graft. This was one of my earlier cases, wherein the central sutures were much less numerous than the number of sutures I now introduce. The remaining 108 patients have grafts that have good colour match, texture, surface regularity, and pliability (Fig. 3).

Discussion

Of the many requisites for successful skin grafting—apart from surgical competence—perhaps the most important single factor to ensure a good 'take' is the maintenance of a firm and constant approximation between the graft and the recipient bed for the first postoperative week. It is equally important to immobilise the graft in its bed to prevent the formation of haematoma by avulsion of the newly sprouting fronds of fragile vascular tissue. One of the main causes of failure of a free graft is the formation of haematoma underneath it.

All methods of securing free full-thickness grafts to the recipient bed as currently practised by various oculoplastic surgeons utilise the principle of continued impaction of the graft to its bed by an extrinisic mechanical device—for example, cotton-wool bolus, Teflon roll, sponge, stent, tinfoil, or other conformers—retained by tie-over sutures (Mustardé, 1966; Mustardé *et al.*, 1970; Fox, 1976; Reeh *et al.*, 1976; Smith, 1976; Soll, 1976; Tenzel, 1976). Such fixation devices are helpful on convex surfaces. But on concavites, for example, the medical canthus and surrounding area (where the majority of basal cell tumours occur), and especially the sites where there is no rigid skeleton against which external pressure can be exerted, for example, in full thickness reconstructions of lower eyelids with double free grafts, external fixation devices cannot be relied on. A further drawback to these fixation devices is the need to admit patients to the hospital, so that their activity after the operation can be restricted. The larger the graft, the more the restrictions.

It would appear that the ideal technique for fixation of a free graft should provide intrinsic fixation—an intraoperative transfixion that can be maintained until cuto-cutaneous union occurs—without any reliance on external factors to maintain the graft-to-bed approximation. These criteria are fulfilled by the central and paracentral sutures described in my technique (Fig. 1).

This central fixation technique would appear to have the following advantages over the tie-over bolus technique: (1) Free dermal grafts of much larger size can be utilised, thus eliminating the need to use local pedicle flaps, which have their disadvantages. (2) Grafts of irregular shapes in awkward sites like the nasocanthal region or the outer canthus can be utilised with excellent results. (3) Assured constant approximation and immobility of the graft relative to its bed prevents a gap that would otherwise be filled by haematoma and fibroblastic invasion. The ultimate results are therefore of a consistently good quality. (4) As there is no need to restrict the activity of the patient after the operation, surgery can be performed on day case basis.

The theoretical objections that may be raised about this technique are that the central sutures may provoke a foreign body reaction resulting in formation of granuloma in the recipient bed, or that they may provide a track for epithelial cells to migrate to the recipient bed and thus put the graft in jeopardy. Neither of these phenomena have been encountered in any of the 109 patients reviewed for this communication.

So far as the suture material is concerned, after extensive experience I have come to regard 5–0 polyglycolic acid suture material (Dexon) as the most suitable among those currently available, but think that a thinner suture (6–0) of Dexon on a similar needle (11 mm, three-eights circle) would perhaps be more suitable. The advantage of Dexon over silk is that Dexon is better able to hold the wound edges, as the knots do not slip. However, the

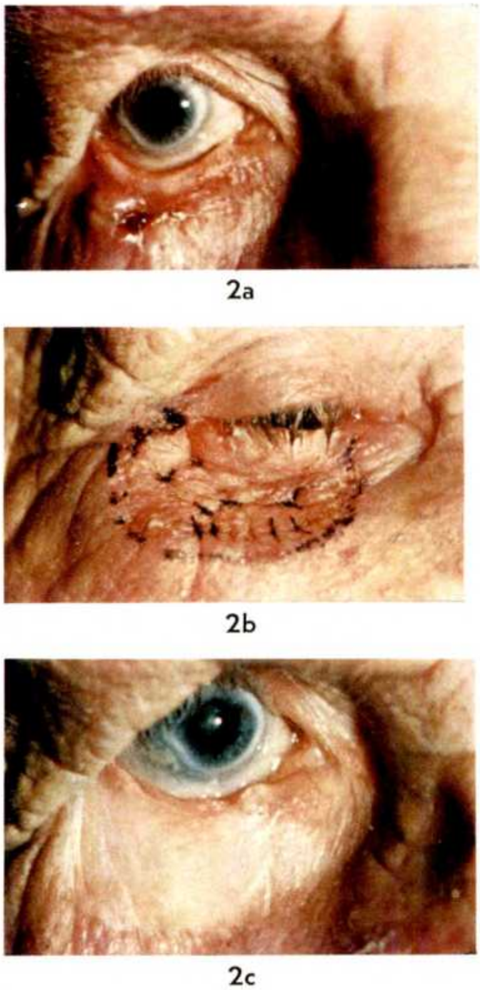
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Fig. 2 *Rodent ulcer involving the right lower eyelid of an 86-year-old female. Nearly three-quarters of the lower eyelid was excised in full-thickness, and the reconstruction carried out with free buccal mucosal and free skin graft. Note absence of 'central' sutures near lid margin, and also that the central sutures are not so numerous as I now insert. Paucity of central sutures has resulted in less than satisfactory end result—there is sagging of the new lid margin, and poor colour match of the graft.*
(a) *Preoperative.* (b) *Immediate postoperative.*
(c) *Appearance 9 months after surgery*

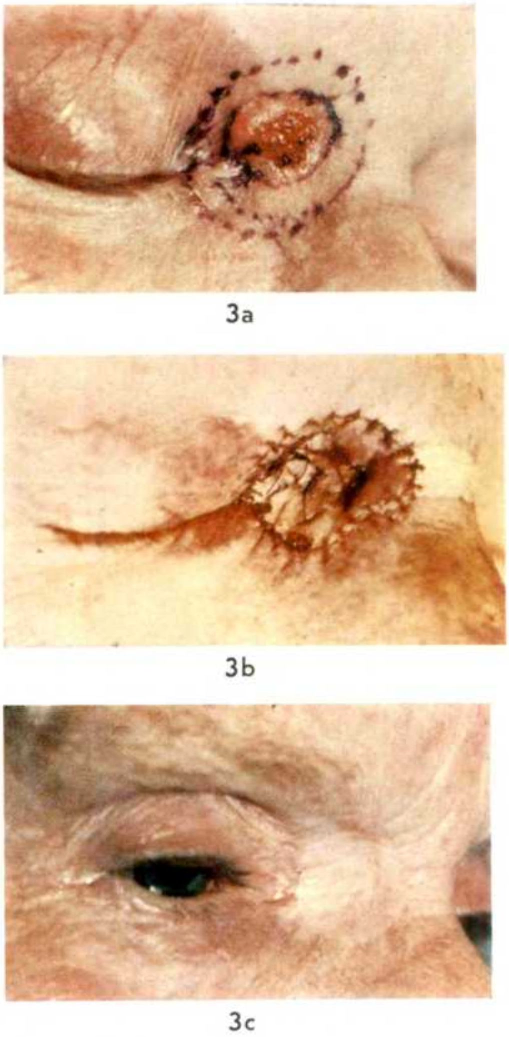
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Fig. 3 (a) *Preoperative appearance of rodent ulcer at the inner canthus. Proposed excision along the outer markings.* (b) *Immediate postoperative appearance showing the marginal and central sutures securing the graft.* (c) *Appearance 6 months after surgery, showing a satisfactory graft with good colour match, texture and surface* disadvantage of Dexon is that the sutures are a little more difficult to remove than the silk sutures. Their removal is best achieved with the heel of a No. 15 Bard-Parker blade.

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Ankyloblepharon filiforme adnatum

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SUMMARY Two cases of ankyloblepharon filiforme adnatum in siblings are presented. One sib had associated cleft lip and palate, the other had bilateral syndactyly of the second and third toes. Father, paternal grandmother, and great-grandmother all had bilateral syndactyly of the second and third toes. Cases of ankyloblepharon filiforme adnatum reported in the ophthalmic literature are reviewed as are cases of ankyloblepharon occurring as part of the popliteal pterygium syndrome. It is postulated that the association of ankyloblepharon with other abnormalities may be part of the spectrum of the popliteal pterygium syndrome with autosomal dominant inheritance, incomplete penetrance, and variable expressivity.

Ankyloblepharon filiforme adnatum (AFA) is a rare benign congenital abnormality. A more than chance association with other congenital abnormalities and occurrence in siblings make the study of pedigrees of affected individuals of interest in trying to ascertain the heritability of the condition.

Case report

This girl was born on August 6 1977, the result of a normal full-term pregnancy. Her mother denied taking any drugs during the first trimester. At birth the baby was noted to have 'fused' eyelids as well as bilateral cleft lip and palate (Fig. 1*a*, *b*). Cardiac auscultation revealed a systolic murmur which disappeared by the second day and was thought to represent a closing ductus arteriosus.

More detailed ophthalmic examination showed that there were 2 asymmetrical adhesions between each pair of eyelids; these were easily parted with a strabismus hook. The manoeuvre was accompanied by minimal bleeding along the grey line of each eyelid (Fig. 2*a*, *b*). The vestigial remnants on the eyelid margins disappeared completely within 48 hours. The cilia and posterior surface of each eyelid were normal, as were the eyes to external examination, ophthalmoscopy, and retinoscopy. Chromosome analysis revealed a normal female karyotype.

The family history had no records of consanguinity. An older brother born on August 19 1973 had bilateral AFA as well as bilateral syndactyly of the second and third toes. The eyelid adhesions were freed by the family physician. There were no other ocular abnormalities. The father has no ocular abnormalities but has similar bilateral syndactyly of the second and third toes. The mother is myopic but is otherwise normal. The paternal grandmother and great grandmother both had bilateral syndactyly of the second and third toes.

Discussion

Ankyloblepharon filiforme adnatum was first described by von Hasner in 1881 (Judge *et al.*, 1929). It occurs in many cases as an isolated anomaly, and the bands may be single or multiple (Duke-Elder, 1964). Associated anomalies have included cleft lip and palate (Khanna, 1957; Long and Blandford, 1962; Sood *et al.*, 1968; Ehlers and Jensen, 1970). Neuman and Shulman (1961) described a 3-day-old boy with AFA who had in addition adhesions between the alveolar processes of both upper and lower jaws, a papilla and a sinus on the left side of the lower lip, and a cleft palate. Bilateral syndactyly of the fourth and fifth toes, partial adherence of the left ear to the skin of the head, and a ventricular septal defect of the membranous type with a patent ductus arteriosus were associated abnormalities reported by Rogers (1961) in a premature baby. More recently Kazarian and Goldstein (1977) have reported a single case of AFA associated with hydrocephalus, meningomyelocele, and imperforate anus.

The histological changes of AFA have been described by many authors; the cause, however, has not been elucidated. A 'familial' tendency was invoked by Howe and Harcourt (1974), who

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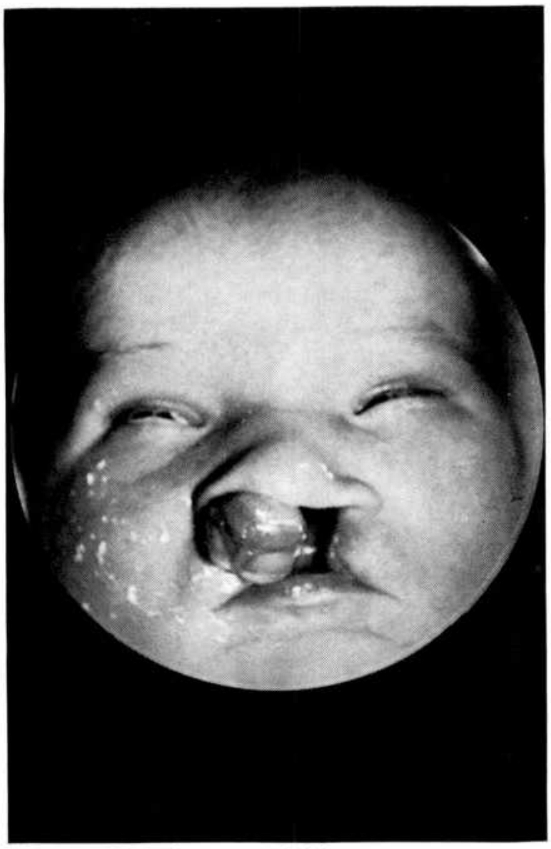

Fig. 1a *Bilateral AFA and cleft lip*

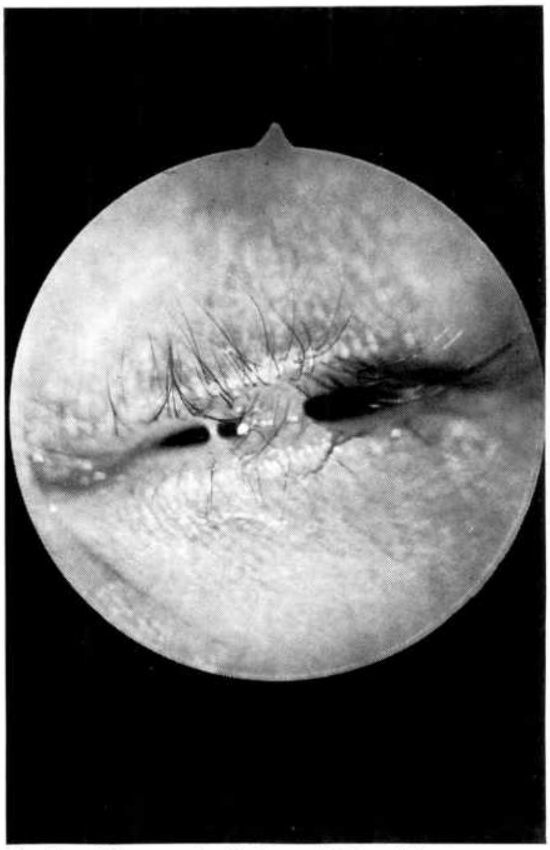

Fig. 1b *Close-up of adhesions of left eyelids*

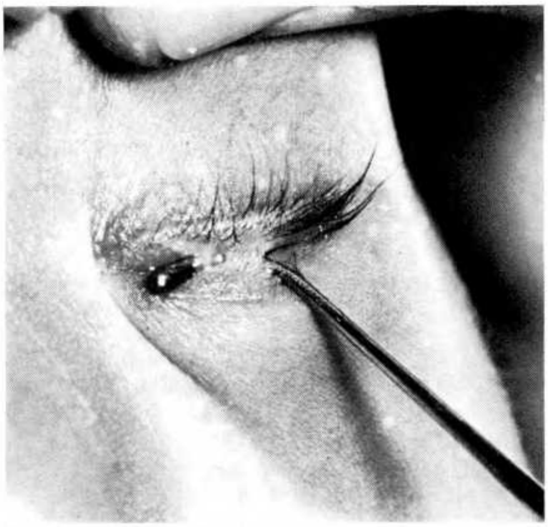

Fig. 2a *Strabismus hook in place prior to separation of left eyelid adhesions*

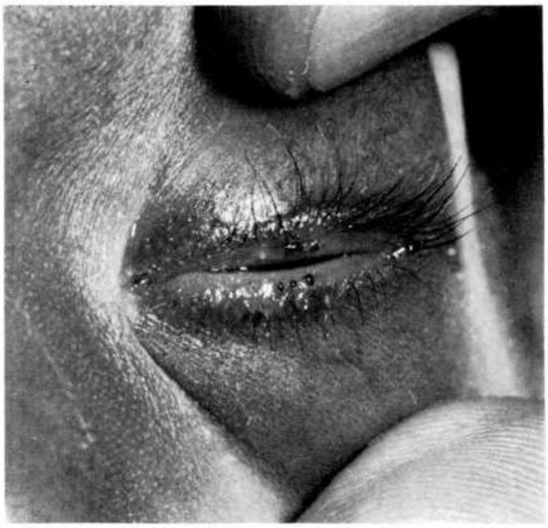

Fig. 2b *Left eyelids showing minimal bleeding along the grey line following separation*

described the condition in identical twins, and by Khanna (1957), who reported the condition in sisters, one of whom had cleft lip and palate. Gorlin *et al.* (1971) stated that 'the association of cleft lip or cleft palate or both and congenital filiforme fusion of the eyelids appears to be inherited as an autosomal dominant trait'.

AFA may occur as part of the popliteal pterygium syndrome. Other features of this syndrome include popliteal pterygia and oral, skeletal, digital, and genitourinary anomalies. Hecht and Jarvinen (1967) described 2 families in whom a mother and 2 of her children were affected. They noted wide variability of expression of the syndrome and postulated autosomal dominant inheritance. Gorlin *et al.* (1968) also suggested that the syndrome was inherited as an autosomal dominant trait with incomplete penetrance and variable expressivity. The same view was expressed in a recent phenotypic and genetic analysis of the popliteal pterygium syndrome by Escobar and Weaver (1978). They reviewed a number of pedigrees and stressed that the few documented familial cases showed a wide variation in gene expression in affected relatives.

We suggest that virtually all the cases of AFA reported in the ophthalmic literature as well as our own 2 cases may be part of the spectrum of the popliteal pterygium syndrome. Like other authors we suggest an autosomal dominant inheritance with incomplete penetrance and variable expressivity. This would have important implications in genetic counselling of the parents of affected offspring.

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Pathology of a unique type of teratoid medulloepithelioma

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SUMMARY A unique teratoid medulloepithelioma showing a conspicuous vascular component with orbital involvement is described.

Case report

CLINICAL HISTORY

A 6-week-old male infant was referred to the Eye Department at Barnsley District General Hospital because of a buphthalmic right eye, present since birth. A retinoblastoma was suspected on clinical examination, and the eye was removed and sent to the Department of Pathology at the Institute of Ophthalmology, London. The remaining eye was normal, and the baby was otherwise apparently fit and healthy.

PATHOLOGICAL EXAMINATION

Naked eye examination revealed a buphthalmic globe with an ectatic limbus inferiorly. A mass was present outside the eye posteriorly below the optic nerve; the iris appeared atrophic. On opening the globe it was noted that the lens was small, there was choroidoretinal atrophy, and the optic nerve head was cupped. No obvious intraocular tumour was apparent.

Histopathological study, however, revealed neoplastic tissue infiltrating the uvea on one side over a wide area, extending from the iris and ciliary body anteriorly to the posterior pole (Fig. 1). Anteriorly, papillary and tubular structures with the formation of large cystic spaces lined by primitive epithelium were seen (Fig. 2*a* and *b*). The stroma was filled with proliferating endothelial cells and there were vascular channels of various sizes, but on the whole small. This tissue had the features of an infantile angioma. There was infiltration of this vascular element through the sclera, and an extraocular angiomatous mass lay posteriorly (Figs. 3 and 4).

There were no histological features to suggest malignancy, but tumour extended to the cut edge, and removal of the orbital component was obviously incomplete. In view of this, and of the infiltrative nature of the lesion, a close follow-up of the case was recommended to the clinician.

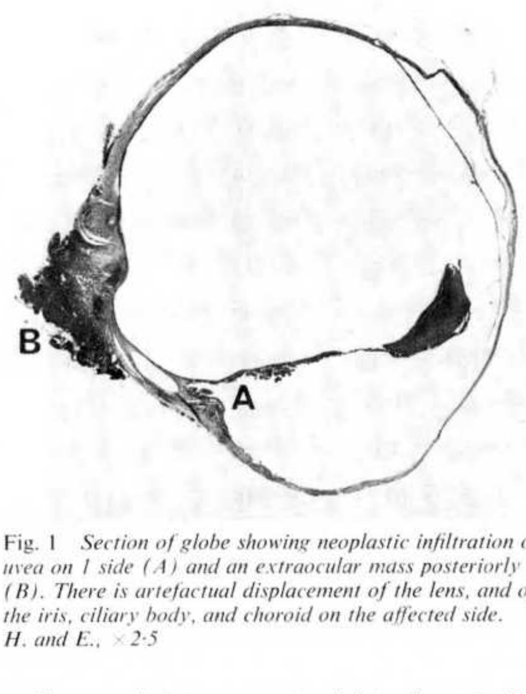

Fig. 1 *Section of globe showing neoplastic infiltration of uvea on 1 side (A) and an extraocular mass posteriorly (B). There is artefactual displacement of the lens, and of the iris, ciliary body, and choroid on the affected side. H. and E., × 2·5*

DIAGNOSIS

Teratoid medulloepithelioma exhibiting a vascular component and with orbital involvement.

Discussion

As was suggested by Zimmerman (1970), tumours of the non-pigmented ciliary epithelium are divided

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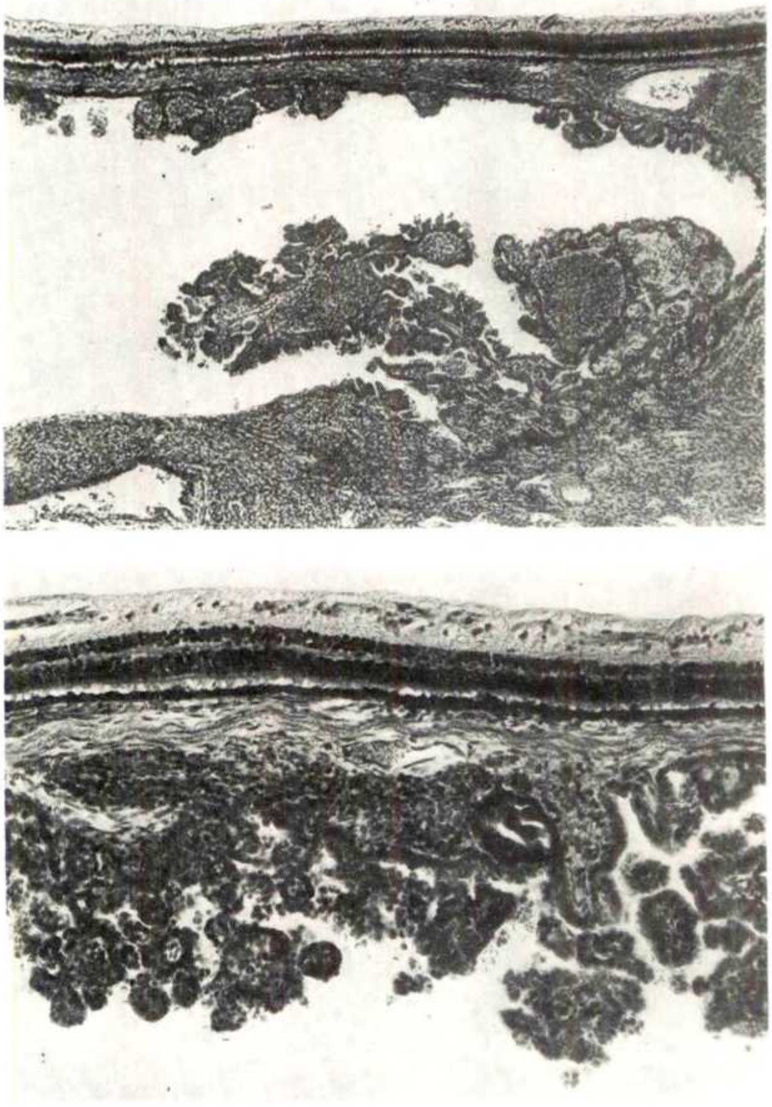

Fig. 2 *Neoplastic infiltration of uveal tissue showing cystic area lined by primitive epithelium exhibiting papillary formation.*

(a) H. and E., × 50

(b) H. and E., × 120

primarily into 2 main groups, namely the embryonal or congenital, and the adult or acquired. Both the benign and malignant varieties of 'pure' and 'teratoid' medulloepitheliomata can be regarded as congenital neoplasms.

The pure type of medulloepithelioma is characterised by the formation of multilayered sheets of undifferentiated cells similar to the primitive medullary epithelium of the optic vesicle. Tubular and papillary structures resembling ciliary epithelium are also formed, and there may in addition be rosette formation, pigment epithelium formation, and differentiation into astrocytic elements. The presence of undifferentiated sheets of neuroblastic cells as seen in retinoblastomata is observed in the malignant varieties of such tumours. Teratoid medulloepitheliomata contain, in addition to the medulloepitheliomatous components, heteroplastic elements, most notably cerebral tissue, hyaline cartilage, and skeletal muscle, which are not normally found in the eye during either embryonic or postnatal development.

The case presented is unique in that while the tumour can be classified as a teratoid medulloepithelioma the presence of a conspicuous vascular element resembling an infantile angioma with

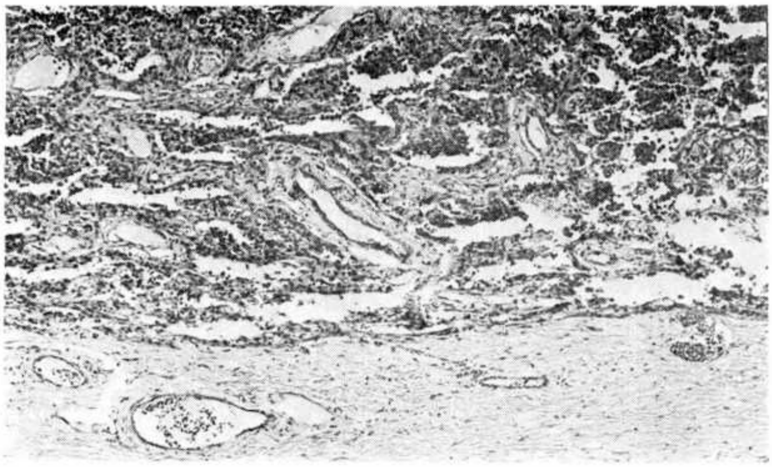

Fig. 3 *Section through sclera and extraocular tumour mass. H. and E.,* × *60*

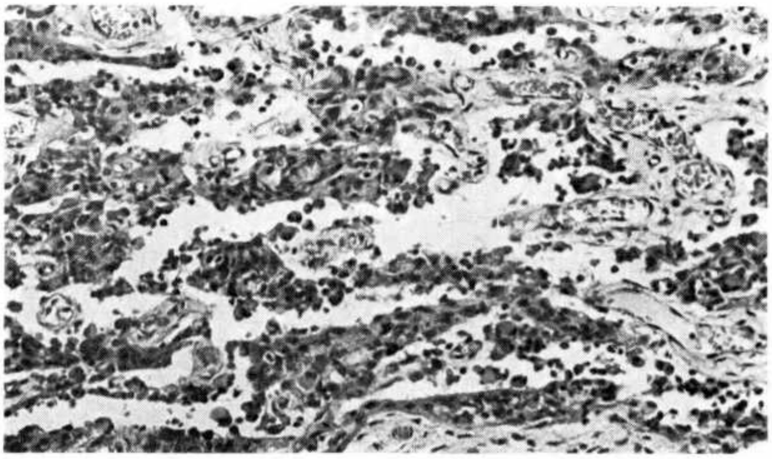

Fig. 4 *Extraocular angiomatous tumour mass. H. and E.,* × *150*

orbital involvement is as far as can be ascertained the first documented report of such an association. It is of interest to speculate that if only the orbital tissue had been submitted for histopathological examination the diagnosis made would have been one of infantile angioma; the presence of a teratoid medulloepithelioma was not suspected until the enucleated eye was fully examined. Zimmerman (1971) has pointed out that a sarcomatous orbital tumour may possibly have originated within the eye, and he cited the example of a chondrosarcomatous neoplasm in the orbit following enucleation of the eye for presumed retinoblastoma. The malignant orbital lesion was considered retrospectively to be part of a teratoid medulloepithelioma, and although there is no histological evidence of malignancy in the case described in this presentation the association of orbital and ocular involvement is not dissimilar.

We wish to thank Mr A. K. Mandal of Barnsley District General Hospital for providing the clinical information, Mr V. J. Elwood and Mr I. Rhodes of the Department of Pathology, Institute of Ophthalmology, for technical assistance, the staff of the Department of Audio-Visual Communications for developing and printing the photomicrographs, and Mrs Audrey Wood for secretarial help.

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British Journal of Ophthalmology, 1979, 63, 135–139

Proton irradiation of malignant melanoma of the ciliary body

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SUMMARY This is our first case of malignant melanoma of the ciliary body treated with proton beam irradiation, a technique that we developed for irradiating choroidal melanomas. After 21 months of follow-up no growth of the tumour has been observed, and shrinkage of the tumour was noted on the follow-up photographs and by ultrasonography. The ^{32}P uptake test, which was positive before treatment, turned negative 14 months after irradiation. The described technique of proton beam irradiation might offer an alternative for the treatment of ciliary body melanomas when the present techniques of iridocyclectomy cannot be applied because of the size of the lesion.

During recent years local excision of certain ciliary body melanomas has provided an attractive alternative to enucleation (Stallard, 1964; Muller *et al.*, 1964; Palm and Linder, 1968; Linnic, 1968; Reese *et al.*, 1968; and Vail, 1971). Unfortunately this technique can be applied only to relatively small tumours. A lesion occupying more than 2·5 clock hours usually cannot be safely excised (Muller *et al.*, 1966).

Local irradiation with cobalt-60 plaques has also been used as an alternative treatment but generally has been considered unsatisfactory, and enucleation has often been necessary owing to postirradiation complications (Stallard, 1973). During the last 2 years we have used a high-energy proton beam for the treatment of choroidal melanomas because of the multiple advantages provided by this technique for localising ocular irradiation (Gragoudas *et al.*, 1977). The accuracy and reliability of this method encouraged us to use it for irradiation of those ciliary body melanomas that are considered inoperable with the present techniques of iridocyclectomy. This report presents our first case of malignant melanoma of the ciliary body treated with proton beam irradiation.

Case report

A 57-year-old white woman was examined because of a slight decrease in vision in her left eye over the past 6 months. Visual acuity was 6/7·5 in the right eye and 6/12 in the left. Slit-lamp biomicroscopy revealed a protruding mass at the inferior portion of the iris, which was slightly atrophic and hyperpigmented in that area (Fig. 1). Gonioscopy showed that the iris was 'tented up' inferiorly, obscuring part of the angle. After dilatation of the pupil, a raised, lobulated, pigmented mass of the ciliary body was detected, extending from the 5 to the 8 o'clock position. The mass, which pressed against the periphery of the lens inferiorly, had produced cataractous changes (Figs. 2, 3). The view of the inferior retina was not clear owing to the lens changes, but transillumination revealed no extension of the mass beyond the pars plana. Fluorescein angiography using a Goldmann three-mirror lens showed some leakage of the vessels over the tumour, and measurements of the uptake of radioactive phosphorus (^{32}P) showed a 61% greater uptake over the tumour than in the same area of the fellow eye. The dimensions of the tumour, calculated from ultrasound measurements and direct measurements obtained during transillumination, were 8×6·5×3 mm. Owing to the large size of the lesion, iridocyclectomy was deemed very difficult, and treatment by proton irradiation was advised.

Design of proton irradiation field and treatment plan

Since the lesion was in the anterior half of the eye and relatively superficial, it lent itself well to an irradiation *en face* with a single proton beam. The

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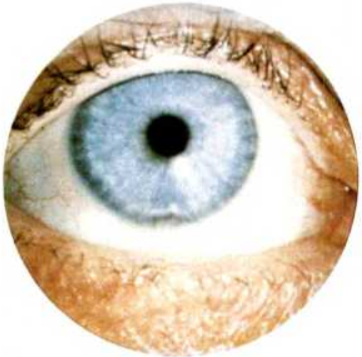

Fig. 1 *Atrophy of the iris at the 6-o'clock position, surrounded by hyperpigmentation*

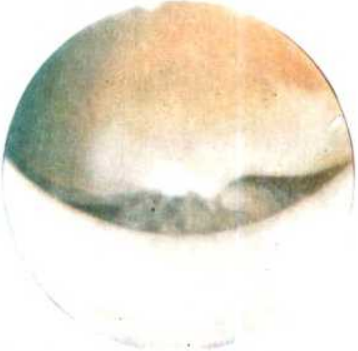

Fig. 2 *Lobulated pigmented mass pressing against the periphery of the lens, producing localised cataract, as seen after pupillary dilatation*

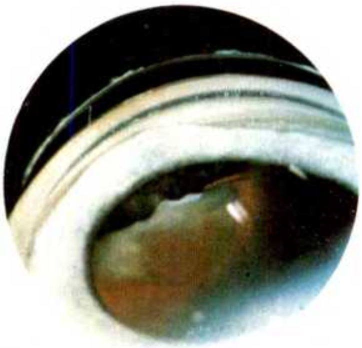

Fig. 3 *Lesion, lens changes, and elevated iris as seen on gonioscopy after pupillary dilatation*

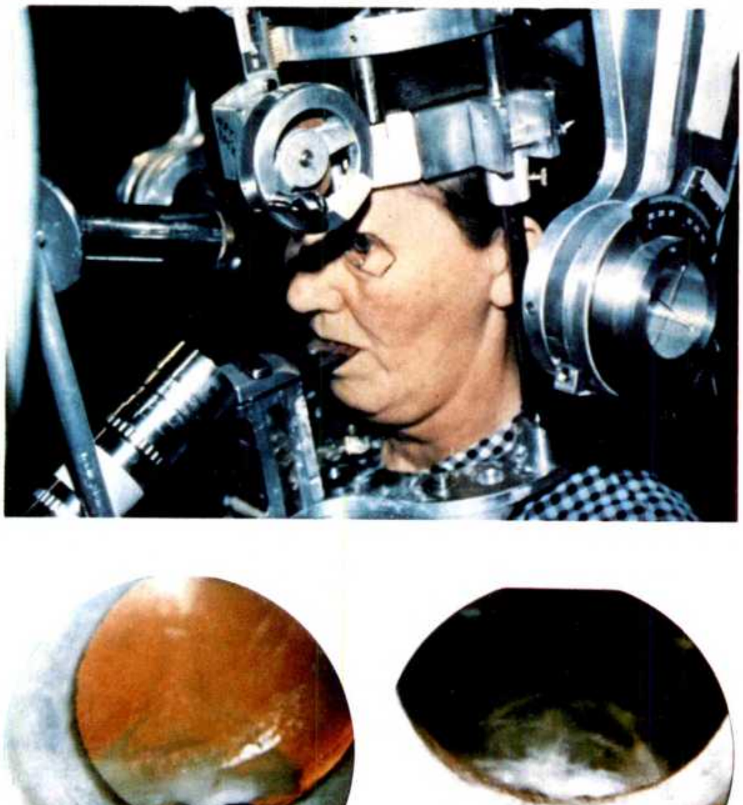

Fig. 6 *Patient in the headholder, looking at the fixation light. Television camera provides magnified image of patient's eye in the control area*

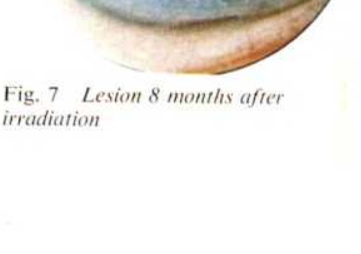

Fig. 7 *Lesion 8 months after irradiation*

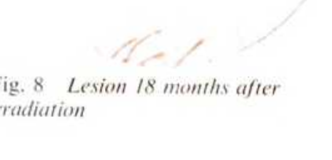

Fig. 8 *Lesion 18 months after irradiation*

patient's head was rotated downward and her gaze directed upward in order to bring the lesion clear of the lower eyelid and to allow the proton beam, which is constrained to the horizontal direction, to be more closely perpendicular to the tumour. The proton penetration was selected so that the distal 90% isodose would be achieved 5 mm from the surface of the eye. Since the lesion was superficial, a single Bragg peak was sufficient to assure uniform dose distribution throughout the tumour volume, and modulation of the depth of penetration, which is commonly employed in our practice (Gragoudas *et al.*, 1977), was not necessary.

We are able to design fields of almost any cross-section by fabrication of appropriate apertures (Gragoudas *et al.*, 1977). In the case of this patient a circular beam seemed highly appropriate. Because the angle between the proton beam and the axis of the eye was approximately 23°, the shape of the beam projected on to the plane containing the lens and ciliary body was slightly elliptical. Fig. 4 indicates the 20, 50, and 90% isodose curves in this plane. The dose distribution achieved in a sagittal plane is indicated in Fig. 5. in which the same isodose levels are shown. The treatment volume is essentially that enclosed by the line labelled '90' in these figures. In the design of the field, margins of 2 mm superiorly and inferiorly and 3 mm laterally were allowed between the tumour and the 90% isodose curves to allow for microscopic extension of the lesion, motion during treatment, and alignment error. This margin is greater than that conventionally used by us in the treatment of choroidal melanomas, where we are able to take advantage of radiopaque markers that are precisely located relative to the macroscopically visible tumour (Gragoudas *et al.*, 1977). In irradiating ciliary body lesion the alignment procedure was guided by visual anatomical landmarks located in the iris and conjunctiva and defined on the ocular surface previously by transillumination.

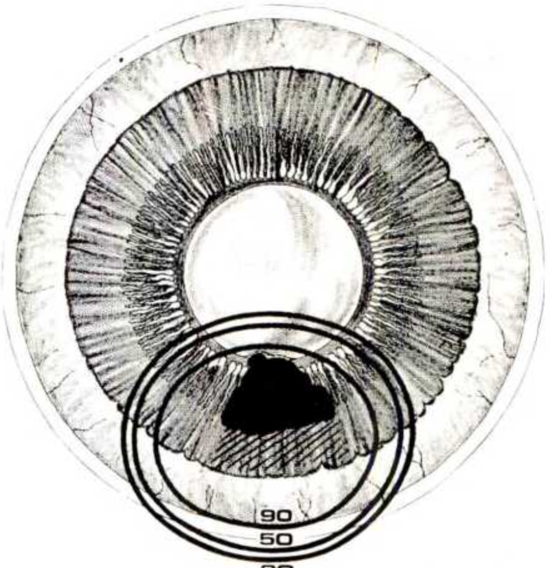

Fig. 4 *Isodose lines demonstrating the irradiated ocular tissues with 20, 50, and 90% of the total dose. Diagram shows ciliary body and tumour; black part represents gross tumour, and diagonal lines indicate area of possible tumour extension*

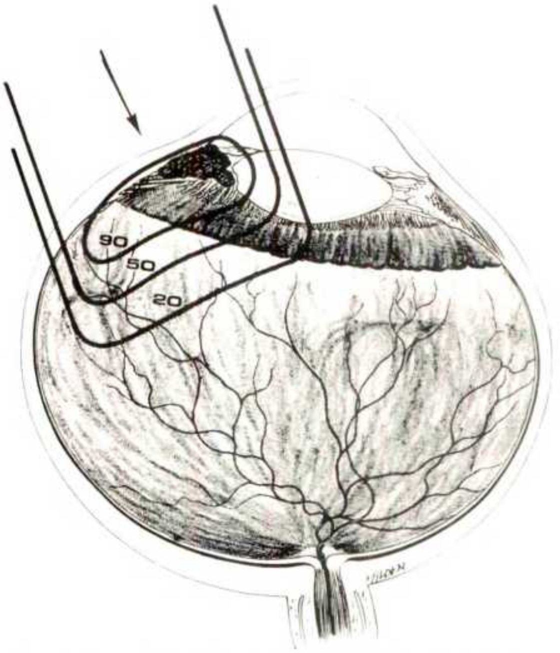

Fig. 5 *Dose distribution curves shown in a sagittal plane*

PROTON BEAM COLLIMATION AND DOSIMETRY

The 160-MeV proton beam generated by the Harvard cyclotron has been described in detail previously (Kjellberg and Klinian, 1975). Briefly, an attenuator is placed in the path of the beam, both degrading the energy to achieve the desired penetration within the eye and scattering the pencil beam to achieve uniform irradiation over the field. The protons are then permitted a flight path of approximately 90 cm, during which secondary collimation reduces the possibility of scattered protons reaching the patient. Dual transmission ionisation chambers monitor the beam during treatment, and the final collimation is achieved by use of a brass aperture 100 cm downstream from the initial degrader. The dose distribution of the beam in a water phantom is measured by scanning in depth and traverse to the beam using a silicon diode (Koehler, 1967). The absolute dosimetry is established by an intercalibration of the diode with a Faraday cup (Koehler, 1967).

PATIENT IMMOBILISATION AND ALIGNMENT

The patient's head was immobilised and held in position in a prototype head holder (Gragoudas *et al.*, 1977). This allows controlled movement of the head in 3 orthogonal directions together with rotation about 2 orthogonal axes. It is thereby possible to bring the lesion to the centre of the axis of rotation and to make orthogonal adjustments of the lesion relative to the proton beam. A narrow light beam of 2 mm diameter coaxial with the central axis of the proton beam was used to position the tumour relative to the beam. The tumour margins were previously defined on the ocular surface by transillumination in relation to anatomical landmarks of the iris and conjunctiva. Immobilisation of the eye was achieved by voluntary fixation during treatment, which maintained precise alignment of the tumour and the beam (Fig. 6). Eye position was continuously monitored by a closed-circuit television monitor (Gragoudas *et al.*, 1977); no more than 0·5 mm of motion was allowed. The patient received a total of 4750 rads given in 5 fractions over a period of 9 days.

Follow-up

The patient was examined after completion of the treatment, then after 1 month, and subsequently at 3-month intervals. No growth of the lesion has been observed after 21 months of follow-up, and signs of regression are evident. Alterations of the tumour pigmentation were observed 4 months after irradiation, and decrease in the height of the tumour was found on follow-up (Figs. 7, 8) and ultrasound examinations. A ^{32}P uptake test that was repeated 14 months after irradiation became negative at the 19% level. No ocular or extraocular complications have been observed during the follow-up period, and the patient has no complaints about her ocular and visual function or eye comfort.

Discussion

High-energy proton beams provide a compelling approach to localised ocular irradiation. These accelerated heavy particles have minimal scatter and can be collimated into narrow beams which retain their cross-sectional form during penetration. Their range is finite and energy-dependent, so that almost no radiation is delivered beyond the target. Furthermore, they undergo maximal energy loss through ionisation as they stop, resulting in a characteristic maximum dose, called the Bragg peak, at the end of the beam path.

The precision and reliability of the aiming techniques for ocular irradiation have been shown previously in animals (Constable *et al.*, 1975) and in man (Gragoudas *et al.*, 1977). Fractionation of the dose, which increases the tolerance of the normal tissues and permits the delivery of higher doses to the tumour, is feasible with this method and has been used in the treatment of choroidal melanomas (Gragoudas *et al.*, 1977). In addition, the possible presence of resistant hypoxic tumour cells renders fractionation of radiation advantageous. Although no increase in the lens opacities of the treated eye have been noted in our patient, cataract formation seems probable considering the dose used. However, it is likely that the opacities will be eccentric and not progressive, thus obviating the necessity of surgery (Stallard, 1968). Only further experience with a large number of treated cases can clarify this question. The limitations of iridocyclectomy and the problems encountered with other forms of localised irradiation make the use of the proton beam technique attractive for the treatment of ciliary body melanomas.

This investigation was supported by Public Health Service Research Grant 5-R01-CA-17638-02, from the National Cancer Institute. One of us (M. G.) is supported by a Research Career Development award CA-00251-01, also from the National Cancer Institute.

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Book reviews

Recent Advances in Glaucoma. International Glaucoma Symposium, Prague 1976. Edited by S. Řehák, M. M. Krasnov, and Gillian D. Patterson. 1977. Pp. 295, figs., tables, refs. Springer-Verlag, Berlin (DM78)

This text of 285 pages is a carefully-edited account of the Prague Glaucoma Symposium of 1976. The material, which is divided into 7 chapters, includes papers on haemodynamics, aqueous dynamics, nerve head circulation, surgical prognosis, screening, ocular hypertension, and the laser. There are many papers of great interest from acknowledged masters in the various fields, but these are interspersed with others of less high quality. This is only to be expected in view of the nature of the publication, which is not an integrated textbook but a collection of papers.

Some of the papers are of particular interest and contain fundamental statements of great importance. For example (page 9), Weigelin and Salminen state, 'No conclusive clue can be found in the extensive literature to any relation between perfusion pressure and the prognosis of an individual case of glaucoma'. Their paper alone, which is a masterpiece of close reasoning, would make the book worthwhile and is a worthy introduction to the wealth of material that follows.

This is not a book for the beginner or casual reader, but it is a fascinating document to true enthusiasts on its subject. REDMOND J. H. SMITH

Vertebrate Photoreception. Edited by H. B. Barlow and P. Fatt. 1977. Pp. 379, figs., refs. Academic Press, London (£14·80)

This book consists of 20 short chapters written by the participants at a symposium sponsored by the Rank Prize Funds in 1976. A dozen chapters are concerned with the electrophysiology of receptor cells, a subject which has received intensive investigation since the technique was pioneered by Tomita in the early 1960s. The volume, power, and quality of work currently in progress make it likely that visual transduction in vertebrate photoreceptors will be a solved problem in biophysical terms in a couple of decades. Other chapters are concerned with photochemistry, the molecular structure of the disc membrane, quantum efficiency, and visual noise.

This is a well-produced book, containing a number of useful summary chapters, each with a short bibliography. It provides a useful text for libraries of visual science and will be of value to advanced undergraduate students. It will be of interest to compare this book with a successor volume produced in 10 years' time. Perhaps by then the elusive 'internal transmitter' (which links primary photosensitive events in the disc to the outer segment permeability changes) will have been identified, and the nature and number of the membrane conductance changes will be understood. A. L. HOLDEN

Augenchirurgie. By Georg Eisner. 1978. Pp. 184, figs., tables. Springer-Verlag, New York (DM120)

Few surgical textbooks set out to describe the basic principles of operative techniques. Rather they tend to concentrate on surgical methods and the anatomy of operations. This volume by Eisner describes in detail the mechanics of instruments and how the design influences their action. The common ophthalmic operations are discussed on this basis, and the student embarking on a career in ophthalmic surgery will be able to learn step by step the principles of surgery ranging from incision techniques and suturing to the finer points of cataract extraction and corneal grafting.

A slight criticism could be that the author tends to make too much of a science out of what is regarded by most as an art, but the book is highly recommended for all beginners in ophthalmic surgery and will make useful reading for surgeons and operating nurses alike. An English translation would be most welcome. T. J. FFYTCHE

Fehler bei Untersuchungsmethoden Diagnostische Irrtümer. 49. Versammlung der Vereinigung Rhein-Mainischer Argenärzte. By Herausgegeben von Wolfgang Straub and Otto Remler. 1978. Pp. 198, figs., refs., tables. Ferdinand Enke Verlag, Stuttgart (DM49)

The subject of 'diagnostic errors' was discussed at an ophthalmic meeting in Marburg in 1976, and the encouraging response to the content and presentation of the subject stimulated the publication of this interesting volume. The book is a natural epilogue to any comprehensive ophthalmic review because it contains examples of the common and less common mistakes in ophthalmic diagnosis, and as much can be learned from these as from any other demonstration.

A total of 33 short articles by different authors are presented covering a wide range of ophthalmic topics viewed from this novel angle. Some of the papers are anecdotal, but many deal with fundamental diagnostic problems, and there is much to be derived from their study. Pathological as well as clinical mistakes are discussed, and all articles are thoughtfully provided with a short English summary. This book of ophthalmic cautionary tales will make pleasant reading for a few evenings for all ophthalmologists who can learn from other people's mistakes. T. J. FFYTCHE

Textbook of Ophthalmology. 9th edn. Edited by Harold G. Scheie and Daniel M. Albert. 1977. Pp. 616, figs., tables, refs. Saunders, London (£19·50)

This is the ninth edition of Sanford Gifford's *Textbook of Ophthalmology*. It was first published in 1938 with the intention of providing a book that would be useful to medical students and general physicians. It is important at the outset to realise that the book is not intended for specialist ophthalmologists but rather as a reference book on diseases of the eye in its relationship to general disease.

The 2 editors and 8 other contributors have combined to produce a work which faithfully fulfils Gifford's original purpose and gives excellent accounts of the more recent diagnostic procedures, such as ultrasound and fluorescein angiography, together with informative sections on the basic sciences in ophthalmoscopy, pharmacology, and genetics. The great strength of the book, however, lies in its medical ophthalmology chapters, and there is a wealth of information on some of the rarer diseases and little-known syndromes of childhood. Numerous tables provide diagnostic data, and at the end of each chapter are a number of key references. The illustrations are in the main excellent, though some of the smaller colour pictures lack definition.

Though he will find a clear exposition of glaucoma, the younger specialist ophthalmologist will have to turn to other textbooks for detailed accounts of more local eye conditions such as uveitis, retinal detachment, or cataract, and for the surgery of these conditions.

This is a most interesting and informative book, and should do much to stimulate interest in ophthalmology.

J. H. DOBREE

Surgery of the Eye. By E. D. DORRELL. 1977. Pp. 217, figs., refs. Blackwell, Oxford (£10·50)

This well-written book is primarily of value to trainee ophthalmic surgeons. A comprehensive account of ocular surgery is given in separate chapters, with instructions and descriptions which are brief but explicit while being abundantly illustrated by accompanying monochrome line drawings. Throughout the text the author draws on his extensive experience by pointing out the various pitfalls which may arise during the course of the surgery while, at the same time, he offers advice on measures which may be adopted to combat them. It is to be expected that every surgeon will find some item of technique with which to disagree, and this is indeed so with this book, although happily these individual disagreements are very rare and minor. A well-merited place is assured for this book in both large and small ophthalmic libraries.

IAN M. DUGUID

Orbit Roentgenology. Edited by PETER H. ARGER. 1977. Pp. 274, figs., tables, refs. John Wiley, Chichester (£33·85)

This work is a multiple-author volume edited by Professor Arger, of the University of Pennsylvania, and includes among the contributors many leading experts in the field of ophthalmology and ophthalmic radiology.

The aim of the book is to provide physicians with the information necessary to provide the best possible care for patients with orbital problems. Like many multiple-author works it suffers from some unevenness both in the length of contribution and in quality. Plain *x*-ray changes and computerised tomography of the orbit are now the dominant investigations in orbital disease. These investigations are given rather less prominence in the text than are angiographic studies (carotid arteriography and orbital venography), which are now only required in selected patients. There are also some omissions: for example, there is no chapter on dacryocystography or on the localisation of foreign bodies in the eye by radiography. These are surely needed in a textbook of ophthalmic radiology.

The standard of illustration is excellent, and one would particularly pick out the contributions of Dr Jacqueline Vignaud and her colleagues in this respect: the chapter on the external carotid supply to the orbit is quite suberb, both in text and illustration, though perhaps an over-elaboration in a textbook of this size.

In short, this is a work of mixed quality with many excellent contributions and perhaps most appeal to the specialist radiologist or ophthalmologist. It is too unbalanced to be recommended as a primer on the subject for trainees.

GLYN A. S. LLOYD

Correspondence

Adjunct to tonometry

SIR, I wonder if I could bring to your attention a useful adjunct to tonometry. In cases where one suspects that an eye may be infected, particularly with a virus disease, it is always rather unpleasant to have to use an applanation tonometer because one is well aware of the considerable difficulty in sterilising it afterwards with real confidence.

Back in the 1950s, I recollect that someone in the USA described a device called a Tonofilm which was to be used under a Schiotz tonometer, but I am not aware that this ever became widely used. I find, however, if one takes a small piece of Cling-Film of the sort that is sold in ordinary grocers' shops to wrap sandwiches, etc., one can in fact wrap the end of an applanation tonometer and thus carry out tonometry insulated from the conjunctival secretions. It is necessary to make sure that the film is smoothed down accurately on the plane surface at the contact head of the applanation prism, otherwise a high reading is obtained. If, however, the film is smoothed down carefully the reading appears to be exactly the same as obtained with no film in position. I hope that this little tip may be of assistance to people working particularly in casualty departments, where the danger of cross-infection with virus conditions is sometimes a problem. If it is wished to sterilise the film it can be cut into small squares packed between layers of paper and autoclaved in the usual manner.

REDMOND J. H. SMITH

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Notes

Services to the visually handicapped

A cross-section of workers with visually handicapped persons met at Coventry on the 21–22 October 1978 and resolved to form a single new organisation of individuals of all disciplines working within the field of visual handicap. The general aim of the new association will be to improve total services offered to the visually handicapped. To this end it will unite individual workers of every description. A steering committee has been formed to organise an inaugural meeting to be held at Leicester University on 24–25 March 1979. An invitation is extended to all individuals working in whatever capacity with blind or partially sighted people to attend and contribute their particular expertise to the establishment of this new organisation and ensure its success. Susan Hicks, 89 Park Hill, London SW4, would be glad to hear from anyone interested in attending.

Trial of bifocal glasses

The editor of the *BJO* has received a letter from Mr T. Stuart-Black Kelly proposing a multi-centric trial of bifocal glasses in the management of myopia in childhood. Details are available from T. Stuart-Black Kelly, Royal United Hospital, Bath.

Taurine

An international symposium on the actions of taurine on excitable tissues will be held at the Sheraton-Valley Forge Hotel, King of Prussia, Pennsylvania, USA, on 23 and 24 April 1979. It is being organised by Drs S. I. Baskin (Medical College of Pennsylvania), J. J. Kocsis (Jefferson Medical College, Thomas Jefferson University), and S. W. Schaffer (Hahnemann Medical College), and is co-sponsored by the Physiological Society of Philadelphia and the 3 medical colleges listed above. Scientists from the United States and abroad will present their latest experimental findings in the following programme sessions: 'Molecular and cellular effects of taurine', 'Effects of taurine on the cardiovascular system', 'Effects of taurine on the retina and central nervous system', and 'Clinical aspects of taurine'. For information contact Dr S. I. Baskin, Department of Pharmacology, Medical College of Pennsylvania, 3300 Henry Avenue, Philadelphia, PA 19129, USA.

Microsurgery course

The Department of Clinical Ophthalmology of the Institute of Ophthalmology will be conducting a course in Ophthalmic Microsurgery on 2–4 May 1979. It will be a practical course concerning common intraocular surgical procedures. Fees for the Course will be £80·00, and the *closing date for applications is 20 March 1979*. Application forms and further details may be obtained from Mrs P. M. Usher, Microsurgical Course Secretary, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD.

SEM in ophthalmology

An international meeting will be held in Brest on 22 June 1979 on the use of the scanning electron microscope in ophthalmology. Further information from Dr J. Colin, Service d'Ophtalmology, Centre Hospitalier Régional de Brest, 29279 Brest, Cedex, France.

Retinal disorders

The Wilmer Institute Retinal Vascular Center's 10th anniversary celebration is to be held at Sun Valley, Idaho, on 25 June to 1 July 1980. The topic will be 'A decade of progress in diagnosis and management of retinal vascular and macular disorders'. For additional information write to Stuart L. Fine, MD, Wilmer Institute, Johns Hopkins Hospital, Baltimore, MD 21205, USA.

Jules François prize

This prize will be awarded every 3 years to a research worker who has made an important contribution to ophthalmology. The candidate must be not older than 40 years on 1 January 1980. The amount awarded will be B Fr100 000. Further details from the secretary of the Jules François Foundation, Dr J. D'Haenens, E. Beernaertstraat 34, 8400 Oostende, Belgium.

Training aids on xerophthalmia

Eight prototype training aids for use in the prevention and treatment of xerophthalmia and keratomalacia are available from Helen Keller International, New York. The materials are aimed at health and nutrition personnel at all levels in developing countries. The aids are being used to teach the best methods for eradicating child blindness brought on by malnutrition and lack of vitamin A. The information ranges from latest scientific findings on the clinical diagnosis and treatment of nutritional blindness to simpler guides on the aetiology, prevention, and treatment of the disease, and flip charts for use in teaching mothers the hazards of malnutrition and lack of vitamin A in a child's diet. Filmstrips, slide sets, plates, and illustrations are included. A flimsy, *Conquering Xerophthalmia*, with descriptions of the aid and an order form may be obtained, without charge, by writing to Blindness Prevention Department, Helen Keller International, 22 West 17 Street, New York, New York 10011, USA.

Retinal degenerations

The Retinitis Pigmentosa Foundation plans to take part in the establishment of one or more additional centres for the study of retinitis pigmentosa and of allied retinal degenerations. To that purpose it will entertain grant proposals for research support. In general, programmes should be directed toward a basic understanding of the gene defect or defects responsible for one or more type of hereditary retinal degeneration or towards the acquisition of information on basic retinal function that is prerequisite to such an understanding. Further information from Dennis Hartenstine, Executive Director, Retinitis Pigmentosa Foundation, Rolling Park Building, 8331 Mindale Circle, Baltimore, Md. 21207, USA.

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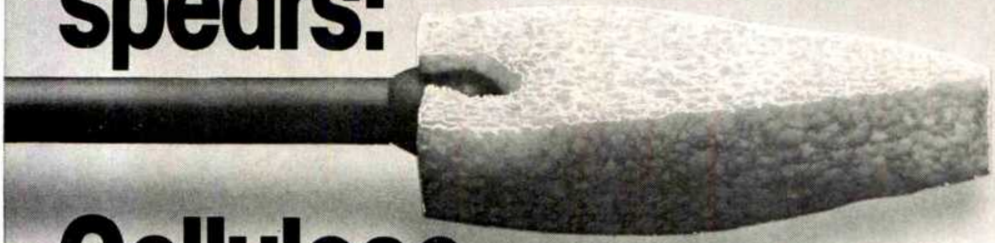

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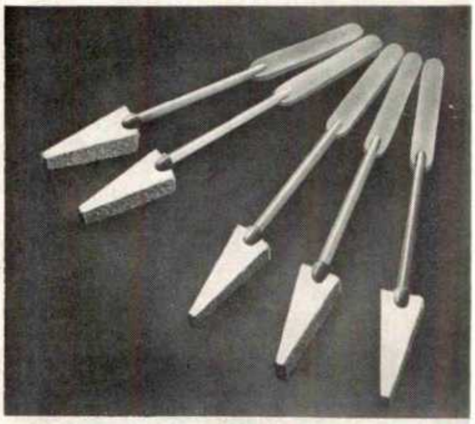

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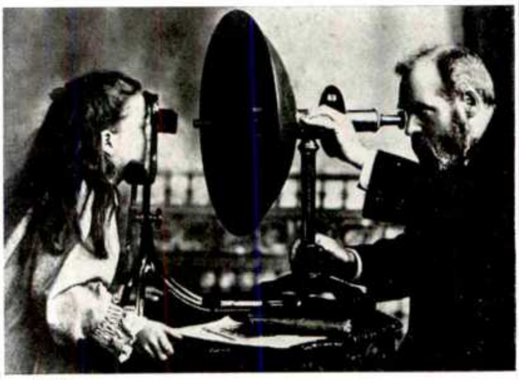

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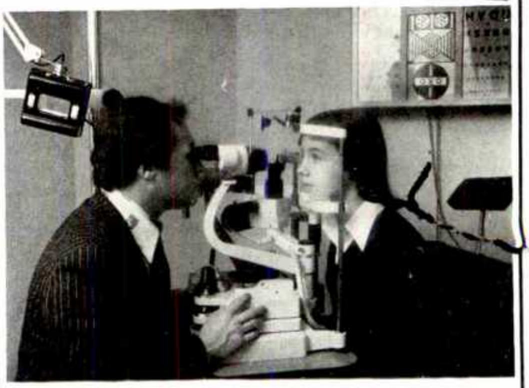

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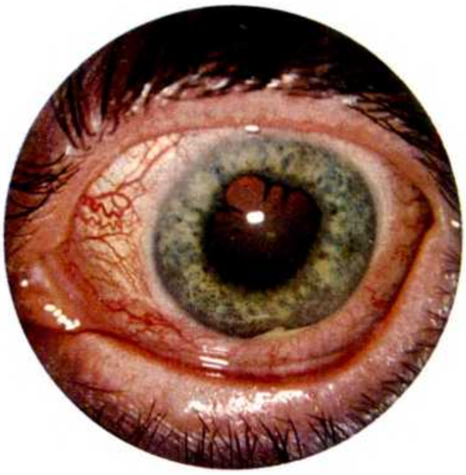

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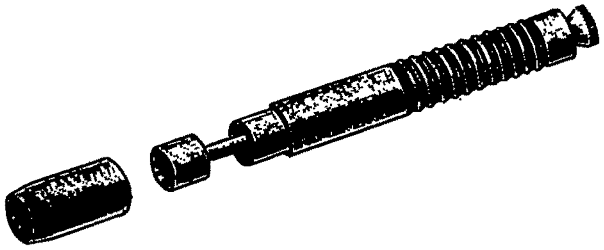

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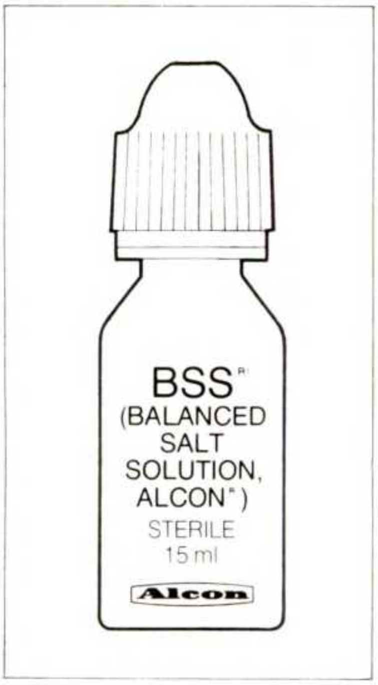

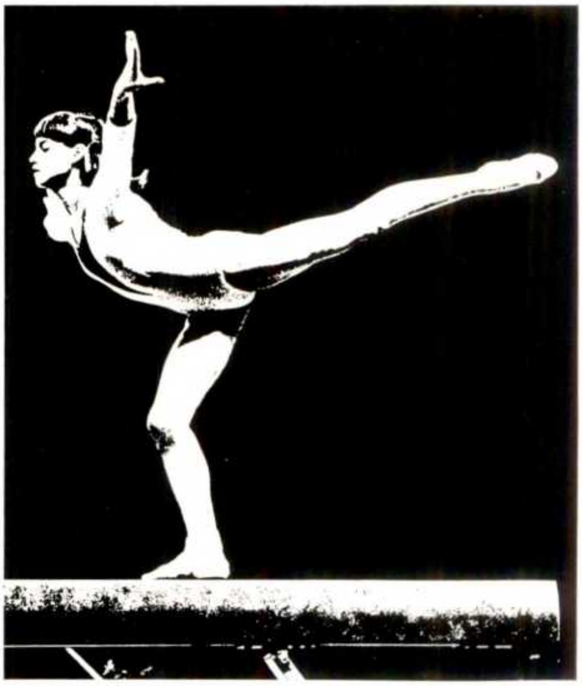

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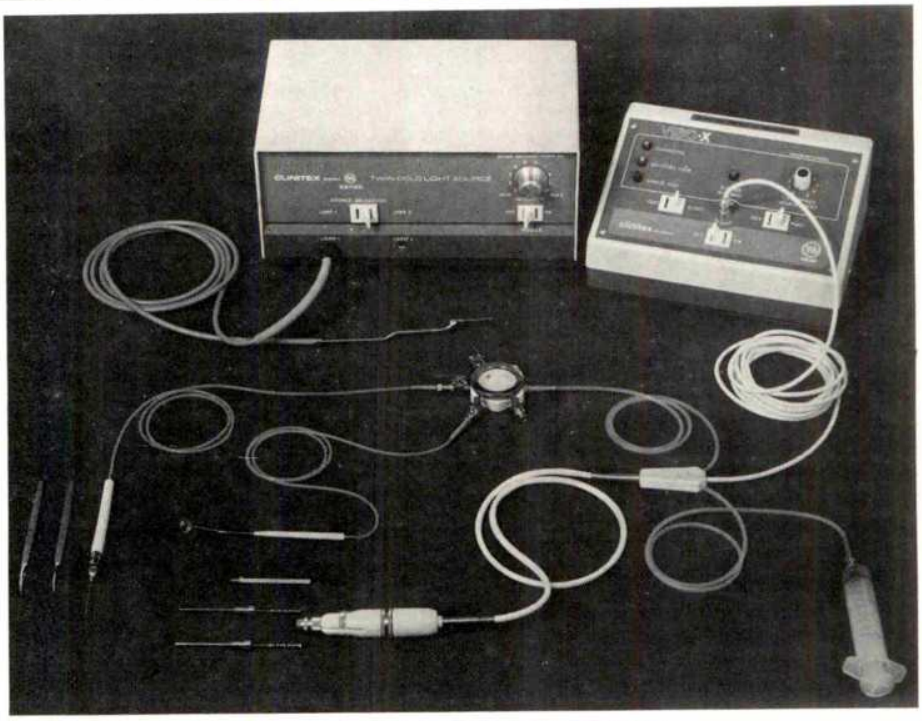

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British Journal of Ophthalmology, 1979, **63**, 143–144

Editorial: Fluorescein angiography of the iris

Papers on iris fluorescein angiography have gradually accumulated over the last 10 years since the first angiograms were reported (Jensen and Lundbaek, 1968a, b), and it therefore is an appropriate time to assess the impact of this investigation on research, diagnosis, and clinical management.

Like the vasculature of the retina and the brain iris capillaries have a non-fenestrated endothelium lined with basement membrane and occasional pericytes. In primates the junctions between the endothelial cells are tight with zonula occludentes (Vegge, 1972). Fluorescein will not diffuse through vessel walls when they are equipped with tight intercellular junctions of this type. Damage to iris capillaries may result from anoxia, alteration in the intra- and extravascular pressure, ischaemia, trauma, and inflammation.

Experimentally it can be used to study the influence of active agents and their antagonists, which can be administered either topically or systemically. Following the discovery by Ambache *et al.* (1965) that a prostaglandin-like substance was released into the rabbit's eye in response to mechanical trauma Eakins *et al.* (1972) showed that prostaglandins were produced in experimental uveitis induced with bovine serum albumin. Whitelocke and Eakins (1973) used fluorescein angiography to demonstrate changes in calibre and permeability of blood vessels in rabbits after topical application of prostaglandins, and reported that the substantial increase in vascular permeability could be reduced by prior treatment with polyphoretin phosphate. Similar techniques have been employed experimentally to study the degenerative release of norepinephrine. This causes transient ocular inflammation, which has been considered to be mediated by prostaglandins, and these can be counteracted with suitable antagonists (Neufeld *et al.*, 1973). Iris angiography would be expected to continue to be of use in similar experimental situations, and in particular such models provide a way in which the efficacy of anti-inflammatory drugs may be tested. It can likewise be used in man to investigate the value of topical therapy of uveitis or postoperative inflammation.

In studies of eye disease many investigators have concentrated on those diseases associated with vascular lesions in an attempt to learn more about the disease process or to investigate the technique as an aid to diagnosis. The vascular responses have now been well documented in a number of pathological conditions, including uveitis (Kottow, 1978), rubeosis iridis (Wong, 1972), the early changes in diabetic microangiopathy (Jensen and Lundbaek, 1968a; Freidburg *et al.*, 1972), occlusive disease of retinal arterioles and venules (Kottow *et al.*, 1976), anterior segment ischaemia (Easty and Chignell, 1973), various types of glaucoma (Vannas, 1969), and postoperative cystoid macular oedema (Kottow and Hendrickson, 1975). Much has been learnt about these diseases, and doubtless other interesting information will be reported in the future.

The causes of iris neovascularisation are numerous (Gartner and Henkind, 1978), and it is helpful to know whether abnormal vessels are present at an early stage in the disease. This is particularly true in patients with central retinal vein occlusion or diabetes with retinopathy. Fluorescein angiography provides a method to detect the early stages which cannot be seen by clinical examination. It allows a prediction of the risk of later development of rubeosis-iridis or thrombotic glaucoma, which can be treated by peripheral retinal ablation (Laatikainen, 1977).

Inflammatory disease of the anterior uvea together with the trauma of various types, including operative trauma, may merely increase vascular permeability, which is difficult to determine by observation alone and can be seen as an increased leakage of fluorescein dye into the anterior chamber. With advances in methods of fluorophotometry, measurement of the concentration of dye in the anterior chamber can be made (Maurice, 1963; Trevor-Smith *et al.*, 1977), which may short-cut the necessity of photographic techniques where quantitative measurements of dye concentration cannot be made.

In short, iris angiography is likely to be of considerable value in the early detection of neovascularisation and will continue to provide one method for the experimental investigation of anti-inflammatory therapy in the laboratory and in clinical trials. In this issue of the *BJO* 3 papers concern iris angiography, where the uses for the technique are amplified. Dr Laatikainen has followed the iris vascular changes in patients with diabetic retinopathy, and as a result has been able to classify precisely the lesions which she has found, providing a system of grading which will be valuable in future studies of possible treatment modalities. In a second contribution she describes the iris vascular response in a group of patients with uveitis. A third paper, by Drs Brovkina and Chichua, concerns the value of angiography in the diagnosis of iris tumours from which histological material was obtained. These 3 papers are an important addition to an expanding field, which has recently been expertly reviewed in a monograph on iris angiography by Kottow (1978).

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Vascular changes in the iris in chronic anterior uveitis

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SUMMARY Vascular changes of the iris were studied in 6 patients with chronic anterior uveitis of varying aetiology by means of fluorescein angiography. In 1 case the angiographic findings of the second eye were compared with the histopathological changes in the fellow eye enucleated earlier because of absolute glaucoma. In the milder cases abnormal superficial vessels were seen mainly in relation to the minor arterial circle of the iris, while in advanced cases a coarse vascular network covered the whole surface of the iris. Both mild and severe changes were found to differ from the arborising type of neovascularisation usually seen in vascular eye diseases. Instead, a resemblance in the vascular pattern was found between some of these cases and eyes with chronic capsular glaucoma. In 1 patient clinical rubeosis seemed to be partly due to dilatation of the pre-existing capillaries rather than true neovascularisation.

Rubeosis iridis is one of the late complications of many vascular, neoplastic, and inflammatory eye diseases (Schulze, 1967; Hoskins, 1974). It has therefore been considered to be a nonspecific reaction of the iris vasculature to a variety of noxious stimuli. Histologically no differences have been found between the appearance of the rubeosis associated with chronic anterior uveitis and that of other eye diseases (Schulze, 1967). Most of the histological studies, however, have been done on eyes enucleated because of secondary neovascular glaucoma so that they are representative of the very late stages of rubeosis. Some peculiarities in the angiographic pattern of the iris have been described in chronic heterochromic iridocyclitis (Cobb and Smith, 1970). In this paper fluorescein angiographic findings of the iris vasculature in chronic anterior uveitis of varying aetiology are reported, and differences in the vascular response of the iris in uveitis and in some other eye diseases are discussed.

Patients and methods

Six patients with clinical rubeosis due to chronic anterior uveitis were studied. There were 2 cases with heterochromic iridocyclitis, 2 cases with rheumatoid arthritis, 1 case with ankylosing spondylitis with bilateral chronic uveitis, and 1 case with phakogenic iridocyclitis due to traumatic cataract and subluxation of the lens. Further details of the patients are presented in Table 1.

The technique used in fluorescein angiography of the iris was described in detail by Vannas (1969) and is to be reviewed briefly by the author (Laatikainen, to be published).

Results

Two cases, Case 1 with heterochromic iridocyclitis (Figs. 1*a*, *b*) and Case 2 with chronic anterior uveitis due to ankylosing spondylitis (Figs. 2*a*, *b*) showed coarse irregular vessels superficially and related to the minor arterial circle of the iris. The superficial network, the arterial circle, and the peripupillary capillaries all leaked fluorescein. In Case 3, with phakogenic uveitis (Figs. 3*a*, *b*), dilated and leaking radial vessels and capillary networks were found mainly around the pupil and in the midstromal portion of the iris. Mild neovascularisation, although not visible in the angiogram, was present in the chamber angle in all these cases. The intraocular pressure was only moderately raised, and it was controlled by medical treatment. The radial vessels were clearly visible, particularly in Case 1, where there was iris atrophy, and they filled regularly in all cases.

In Case 4, with chronic anterior uveitis due to rheumatoid arthritis (Figs. 4*a*, *b*), and in Case 5,

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Table 1 *Clinical features of the patients*

Case no.	*Age/ Sex*	*Duration (yr) and type of causative eye disease*	*Visual acuity right/left*	*IOP (mmHg) right/left*	*Gonioscopy*	*Treatment of glaucoma*
1	59/M	19, Heterochromic iridocyclitis LE	1·0/1·0	15/37	Mild neovascularisation and localised anterior synechiae	Pilocarpine, adrenaline, acetazolamide
2	50/M	8, Chronic uveitis BE	HM/0·5	30/42	Ditto	Adrenaline, acetazolamide
3	52/M	7, Phakogenic iridocyclitis LE	1·0/PL	15/34	Moderate neovascularisation with anterior synechiae	Pilocarpine, acetazolamide, cyclocryocoagulation
4	28/M	4, Chronic anterior uveitis BE	1·0/1·0	30–60/ 30–50	Fibrovascular anterior synechiae > 180°	Filtrating surgery, cyclocryocoagulation
5	36/M	16, Heterochromic iridocyclitis RE	PL/1·0	34–58/16	Broad fibrovascular anterior synechiae	—
6	71/M	29, Recurrent anterior uveitis BE	0·5/—*	40–60/—	Angle closed by fibrous tissue > 180°	Filtrating surgery

RE = right eye, LE = left eye, BE = both eyes, HM = hand movement, PL = perception of light.

with heterochromic iridocyclitis (Figs. 5*a*, *b*), the superficial vascular network covered most of the surface of the iris from the angle to the pupillary margin, showing extensive leakage of the dye in the late phase of the angiogram. In Case 5 ectropion uveae was found on the temporal side. Some of the newly formed vessels had spread over the pigment epithelial seam on to the cataractous lens. In these eyes the radial vessels were less clearly visible because of a sheet of fibrous tissue covering the surface of the iris. Broad fibrovascular synechiae were present in the chamber angle, and the intraocular pressure was high. In Case 4, 5 antiglaucomatous operations have been performed since this angiogram, but within a few weeks of operation the filtration cleft was closed by new fibrous tissue. In spite of increased intraocular pressure no treatment has been required for glaucoma in Case 5, because the eye was comfortable but blind.

In Case 6, with recurrent iridocyclitis and secondary glaucoma due to rheumatoid arthritis, dilated capillaries were seen in relation to the radial

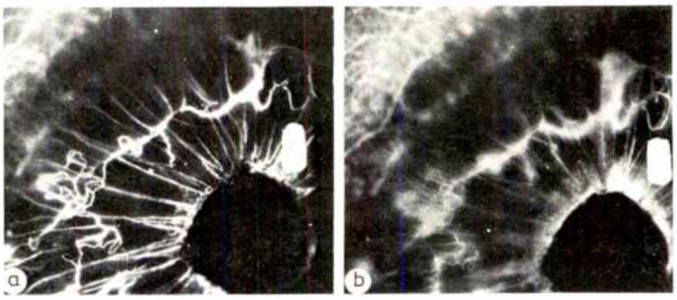


Fig. 1 *Case 1, heterochromic iridocyclitis. Fluorescein angiogram of the left iris. Coarse superficial irregular vessels in relation to the minor arterial circle* (a) *with leakage* (b). *Mild leakage around the pupil* (b). *IOP 37 mmHg*

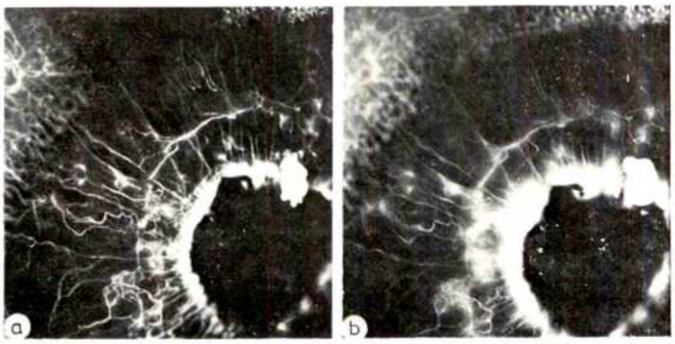


Fig. 2 *Case 2, chronic anterior uveitis due to ankylosing spondylitis. Fluorescein angiogram of the right iris. Coarse superficial vessels particularly in relation to the minor arterial circle* (a) *with mild leakage* (b). *Leakage around the pupil* (b). *IOP 42 mmHg*

Other changes	*Duration and type of causative disease*
Aphakia for 15 yr	—
Posterior subcapsular cataract	Ankylosing spondylitis for 10 yr
Mature cataract and subluxation of the lens	Trauma 47 yr ago
Aphakia RE for 2 yr, LE for 1 yr	Juvenile rheumatoid arthritis for 16 yr
Mature cataract, ectropion uveae	—
Mild posterior subcapsular cataract	Rheumatoid arthritis for 50 yr

* Left eye enucleated because of secondary glaucoma 7 yr earlier.

arteries (Fig. 6*a*). Furthermore these vessels leaked fluorescein (Fig. 6*b*). On this eye trabeculectomy was performed and iris angiography was repeated 1 week later when the intraocular pressure was 10 mmHg. This postoperative angiogram (Figs. 6*c*, *d*) showed further dilatation and leakage of the deep capillaries between the radial vessels, but superficial vessels similar to those seen in the previous cases were not present. In this case the intraocular pressure has been controlled since the operation. Histopathological study of the other eye, enucleated because of absolute glaucoma 7 years earlier, showed peripheral anterior synechiae and mononuclear inflammatory cells in the angle (Fig. 7*a*). In the central part of the iris deposits of dense inflammatory cells with a few small vessels were also present, but dilated capillaries were seen only round the pupil (Fig. 7*b*).

Discussion

The fluorescein angiographic picture of rubeosis iridis seen in the present cases of chronic anterior uveitis differed from that found in various vascular eye diseases (Laatikainen and Blach, 1977; Laatikainen, to be published). In the less advanced cases minute vessels were found crossing the chamber angle, and in addition irregular superficial leaking vessels were present in the area of the minor arterial circle of the iris. Similar angiographic changes were described by Cobb and Smith (1970) in heterochromic iridocyclitis. The present cases showed that this type of capillary network was not specific for heterochromic iridocyclitis but that similar vessels could also be found in other types of chronic anterior uveitis.

Vascular changes described in other anterior segment diseases such as pseudoexfoliation of the lens with or without capsular glaucoma have some similarities with these cases (Vannas, 1969). In

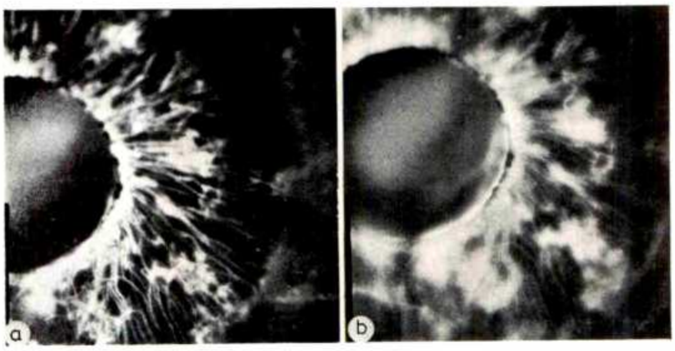
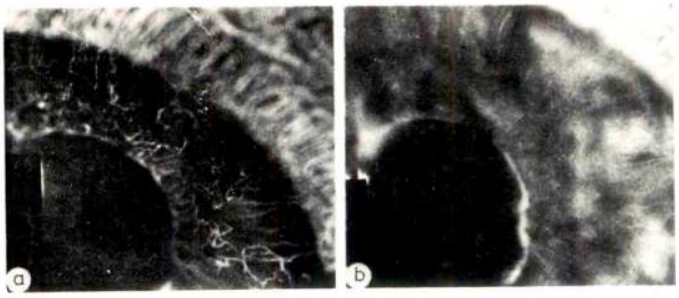


Fig. 3 *Case 3, phakogenic uveitis. Fluorescein angiogram of the left iris. Areas of superficial neovascularisation, particularly in the pupillary part of the iris* (a) *with leakage* (b). *IOP 34 mmHg*

Fig. 4 *Case 4, chronic anterior uveitis due to rheumatoid arthritis. Fluorescein angiogram of the right iris. Delicate newly formed vascular network all over the iris* (a) *with moderate leakage in the late picture* (b). *IOP 30 mmHg*



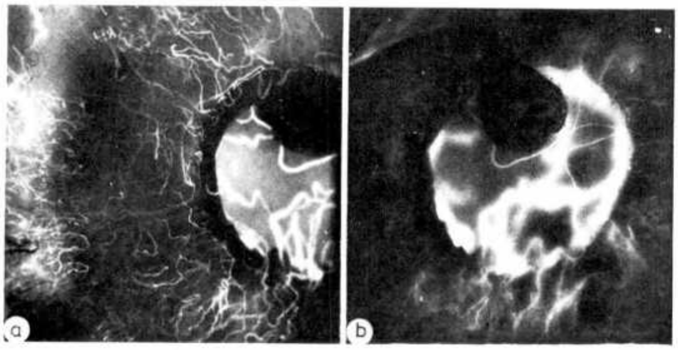


Fig. 5 *Case 5, heterochromic iridocyclitis. Fluorescein angiogram of the right eye. Rich superficial vascular network all over the iris* (a) *with mild leakage in the late picture* (b). *Newly formed vessels cross the pupillary border on to the cataractous lens* (a, b). *IOP 37 mmHg*

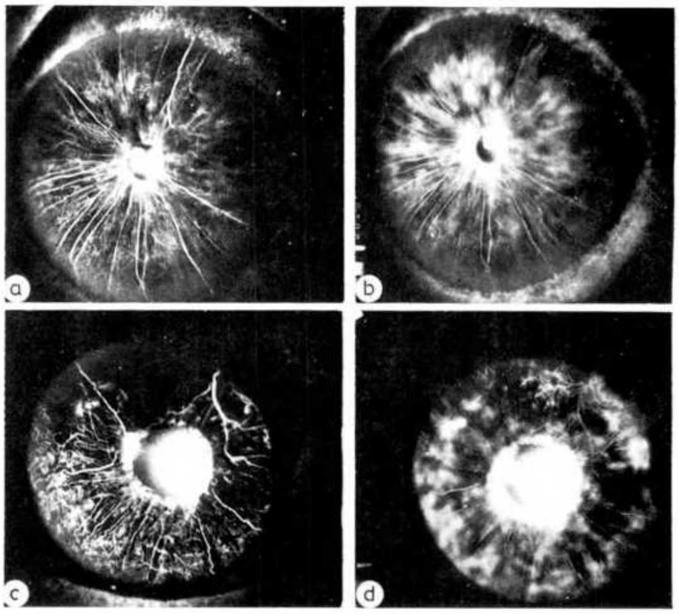


Fig. 6 *Case 6, recurrent anterior uveitis with secondary glaucoma due to rheumatoid arthritis.* a *and* b: *Fluorescein angiogram of the right iris at the time of increased IOP (40 mmHg) showing arborisations of small deep vessels* (a) *which leak fluorescein* (b). c *and* d: *Postoperative angiogram (IOP 10 mmHg) showing further dilatation and leakage of the iris capillaries* (c, d)

contrast, in vascular diseases, neovascularisation of the iris usually appears as arborisations of vessels coming from the angle with or without peripupillary vascular dilatation or neovascularisation, but the midstromal portion is rarely involved early. Early leakage of fluorescein from the circular vessels or vessel loops in the area of the minor arterial circle is common both in inflammatory and in vascular diseases.

As the inflammatory process advances, fibrovascular tissue may gradually cover most of the surface of the iris. In these advanced cases a uniform network of larger mesh of neovascularisation was formed rather than arborisations of vessel trunks such as are usually seen in advanced cases of diabetics (Laatikainen, to be published) or other vascular iridopathies. Similar changes in chronic uveitis have recently been reported by Demeler (1978). Thus it seems that, although histologically indistinguishable, the vascular changes in the iris in localised chronic inflammatory diseases differ in their evolution from those in vascular diseases of the eye. In vascular diseases the pathological process is usually more acute and affects the metabolism of the iris tissue more than in chronic inflammations. Therefore the stimulus for the formation of new vessels is more intense, whereas the formation of fibrous tissue predominates in inflammatory diseases.

It is not always possible to differentiate neovascularisation from dilated vessels clinically or even by fluorescein angiography, because both leak fluorescein. Leakage is more profuse if active inflammation or hypotonia is present, as was seen

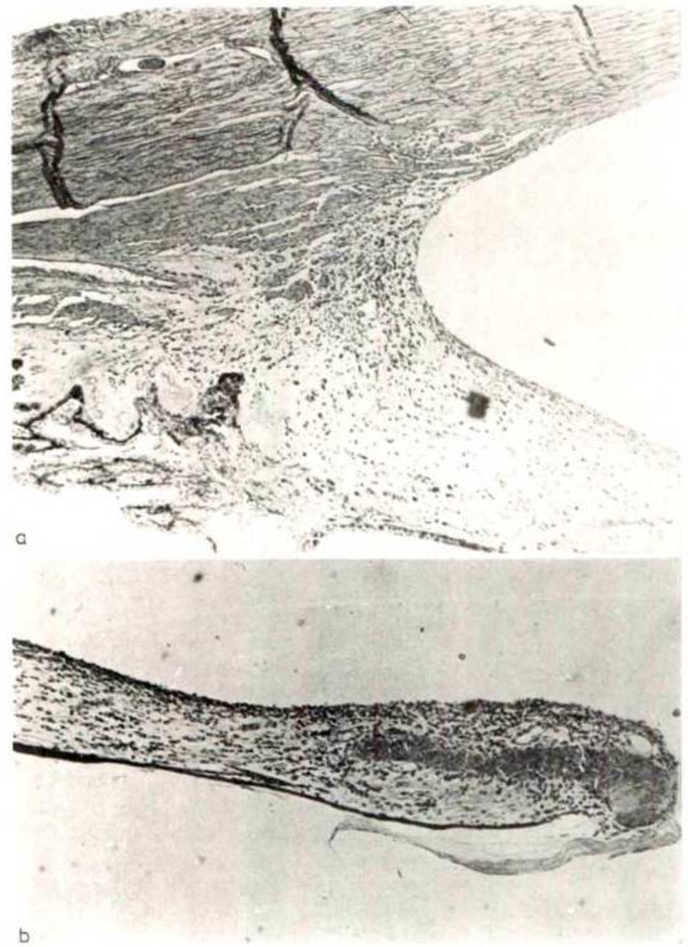


Fig. 7 *Case 6, left eye. Sections from chamber angle* (a) *and central part of the iris* (b). *Anterior synechiae and mononuclear inflammatory cells in the angle* (a). *Dense inflammatory cell deposits and a few vessels in the iris stroma* (b). *Peripupillary capillaries dilated. Remnants of cyclitic membrane on posterior surface. (Haematoxylin and eosin)*

in the post-operative angiogram in Case 6, where some of the leaking vessels were probably dilated capillaries rather than newly formed vessels. This opinion was supported by histological findings in the other eye, where the chamber angle was closed by anterior synechiae, but the number of vessels in the iris was small.

In the second eye of this patient filtering surgery was also more successful than in the other cases where neovascularisation was present on the surface of the iris. In all the other cases the intraocular pressure at the time of angiography was moderately raised. This pressure level may slightly increase the leakage of the superficial networks, because corresponding vessels found in capsular glaucoma have shown less leakage and some of them have even disappeared after return of the intraocular pressure to normal by surgery (unpublished data).

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Development and classification of rubeosis iridis in diabetic eye disease

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SUMMARY The evolution and characteristics of diabetic rubeosis were studied in 33 eyes, and the following vascular abnormalities were found: (1) Dilated leaking capillaries around the pupil; (2) irregular or slow filling of the radial arteries; (3) superficial arborising newly formed vessels, usually starting in the chamber angle; and (4) dilatation and leakage of the radial vessels either before or after the development of neovascular glaucoma. None of the vascular changes was specific for diabetes. Four grades of diabetic iridopathy were distinguished on the extent of rubeosis: I, peripupillary vessel dilatations with leakage; II, early neovascularisation mainly in the chamber angle; III, prominent rubeosis with or without neovascular glaucoma; and IV, florid rubeosis.

Abnormal vessels in the iris in diabetic patients were first observed by Salus (1928), who called the condition rubeosis iridis. Neovascularisation of the iris is often followed by neovascular glaucoma, with its associated blindness and pain. During the last few years more attention has been paid to diabetic rubeosis, because neovascular glaucoma is one of the commonest postoperative complications in diabetic patients after vitrectomy (Michels, 1978).

In this paper the characteristic vascular changes of the iris in diabetic eyes are described, and a classification of diabetic rubeosis is presented.

Patients and methods

Thirty-three eyes with varying severity of diabetic iridopathy were studied by fluorescein angiography of the iris. In many of them several angiographies were performed during the course of the disease at a few months' interval. Each of the patients received thorough ophthalmological examination, including testing of visual acuity, tonometry, biomicroscopy, gonioscopy, and ophthalmoscopy. In most eyes fundus photography and fluorescein angiography were also performed.

In iris fluorescin angiography the technique described in detail by Vannas (1969) was used. A Zeiss-Opton slit lamp coupled with an automatic Robot camera with the filter combination of a Baird Atomic B4 and a Schott GG14 3 mm and the film Kodak Tri-X Pan were used. The photography was begun 10 seconds after the injection of 5 ml of 10% sodium fluorescein (Fluorescite) into the antecubital vein. The pictures were taken at about 2-second intervals.

Results

The following types of vascular abnormalities in the iris were revealed by fluorescein angiography: (1) Dilated leaking vessels around the pupil; (2) irregular or slow filling of the radial arteries; (3) superficial arborising neovascularisation, usually starting in the chamber angle; and (4) dilatation and leakage of the radial vessels, particularly arteries.

On the basis of the angiographic findings 4 grades of diabetic iridopathy were separated.

Grade I. Peripupillary vessel dilatations with leakage. Dilated leaking capillaries around the pupil were the first abnormalities found on the iris angiograms (Fig. 1). Irregularities in the filling of the radial vessels were seen (Fig. 1*a*), but no avascular areas were present. There was no leakage from the radial vessels, but dilated peripupillary capillaries leaked profusely (Fig. 1*b*).

Peripupillary vessel dilatations were either uniocular or more usually binocular. Most of these vessels were also seen by biomicroscopy, particularly in red-free light. Peripupillary changes were also seen in eyes with fairly mild retinopathy, and they have been found to remain unchanged for several years.

Grade II. Early neovascularisation mainly in the

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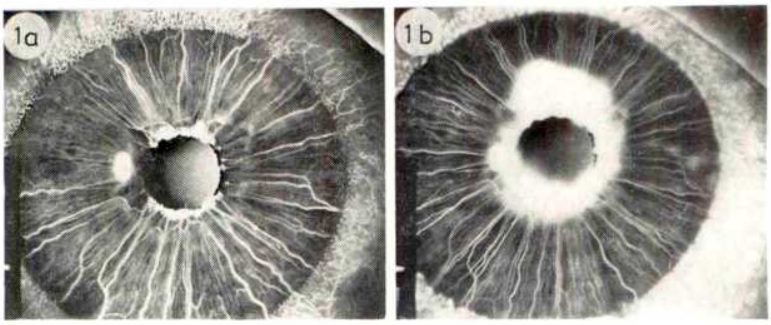

Fig. 1 (a, b) *Fluorescein angiogram of the right iris. Irregular filling of radial arteries and dilated vessels around the pupil* (a). *Marked leakage from peripupillary vessels* (b)

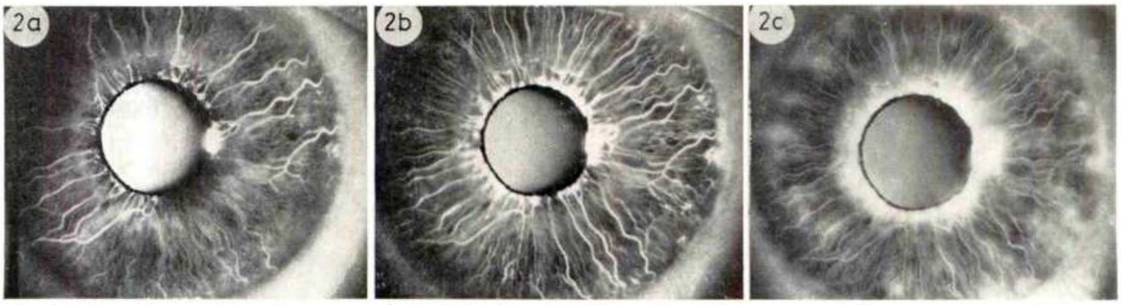

Fig. 2 (a–c) *Fluorescein angiogram of the left iris. Irregular filling of radial arteries and dilated vessels around the pupil* (a). *Early neovascularisation appearing from the angle* (b). *Leakage around the pupil from the new vessels and radial arteries* (c)

chamber angle. In addition to peripupillary vessel dilatations small irregular arborising superficial newly formed vessels appeared in the chamber angle (Figs. 2 and 3*a, b*) and less commonly elsewhere on the iris. These vessels filled in the early arterial phase (Figs. 2*a* and 3*a*) and leaked fluorescein (Figs. 2*c* and 3*b*). Because of their localisation in the angle, the first new vessels were often seen earlier by gonioscopy than on angiograms. Filling of the radial arteries was often irregular (Fig. 2*a*) or slow in all arteries (Fig. 3), and some localised leakage was seen from the radial vessels (Fig. 2*c*).

At this stage most of the angle remained open and the intraocular pressure was normal. In 3 eyes, however, neovascular glaucoma developed before progression of rubeosis further along the iris (Fig. 4*a, b*). In spite of successful trabeculectomy, rubeosis continued its progression in a few months to grade III (Figs. 4*c, d*). All eyes with definite new vessels in the iris also had extensive vascular closure in the retina, and neovascularisation was also found in the fundus either preretinally or on the optic disc.

Grade III. Prominent rubeosis with or without neovascular glaucoma. Arborising new vessels were more prominent and had grown out of the angle covering more of the iris surface (Figs. 3*c–f*, 4*c, d*, and 5). New vessels filled in the early arterial phase (Fig. 3*c*). In some eyes filling of the radial vessels had further slowed down with the progression of rubeosis, and radial arteries were dilated and leaked fluorescein (Figs. 3*e, f*). Thus generalised marked leakage from the main radial vessels was found to precede (Fig. 3*f*) or coincide with (Fig. 4*b*) neovascular glaucoma. After normalisation of the intraocular pressure by surgery leakage from the radial vessels decreased (Fig. 4*d*). In most eyes with prominent rubeosis, however, radial vessels seemed to be less damaged, and only mild leakage of fluorescein was found (Fig. 5).

Most eyes with grade II or III rubeosis had dilated vessels around the pupil (Figs. 3 and 4), but definite new vessels were much less common and less prominent around the pupil than in the chamber angle. Even in some eyes with early neovascular glaucoma there were no certain new vessels except those in the angle (Fig. 4*a*). Mild eversion of the pigmented border or slight deformity of the pupil was, however, often noticed.

In the majority of eyes which developed grade III rubeosis and neovascular glaucoma progression of retinal vascular closure had been extremely rapid, preceding development of rubeosis by only a few months.

Grade IV. Florid rubeosis. In the most advanced

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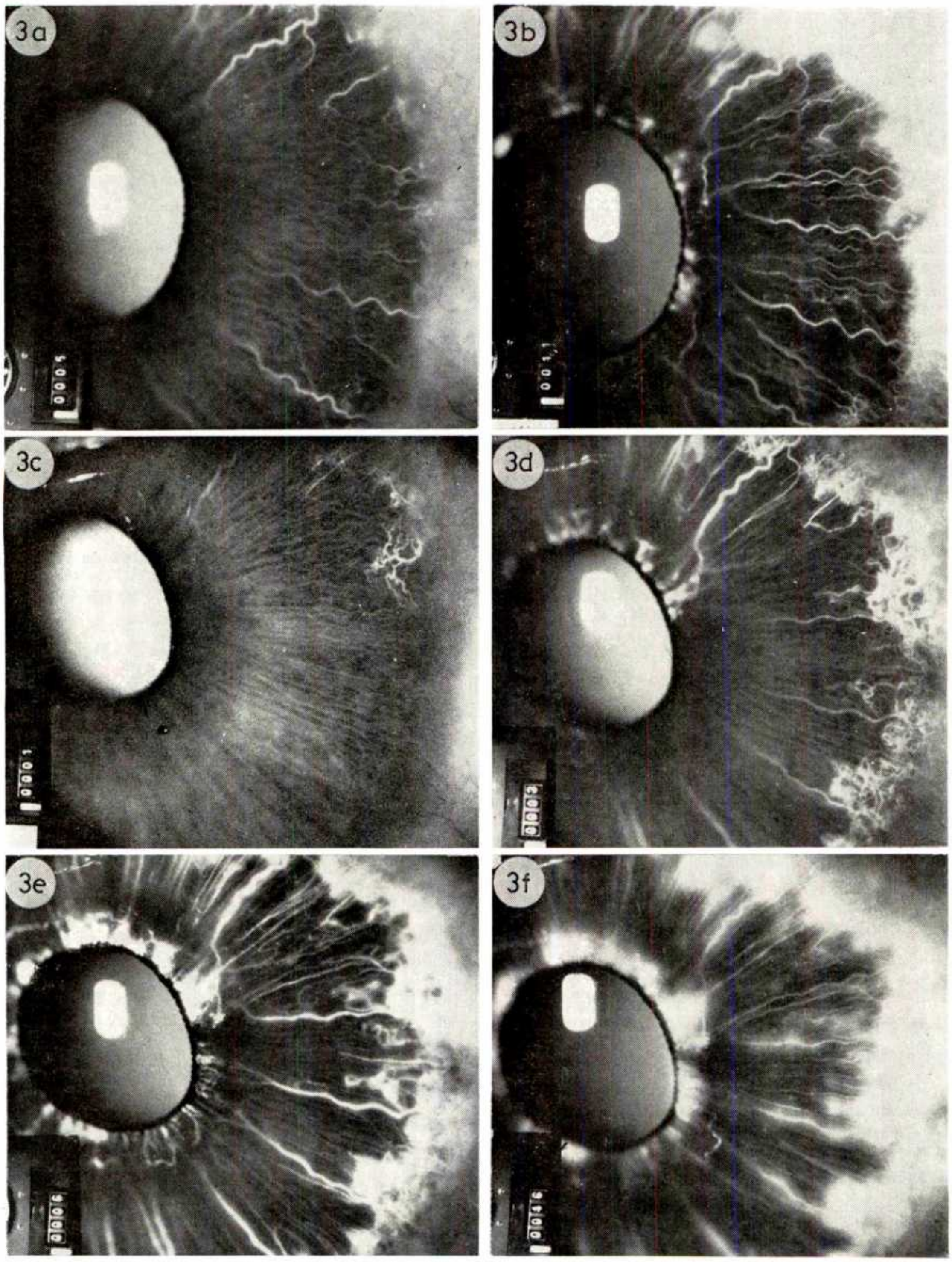

Fig. 3 (a, b) *Fluorescein angiogram of the left iris. Slow filling of radial arteries (about 5 seconds from the iris root to the pupillary border)* (a). *Dilated vessels around the pupil and early neovascularisation in the angle with leakage* (b). (c–f) *Same iris 6 months later. Early filling of new vessels in the angle* (c, d). *Radial arteries and peripupillary vessels dilated with leakage* (e, f). *IOP 15 mmHg. Neovascular glaucoma developed a month later*

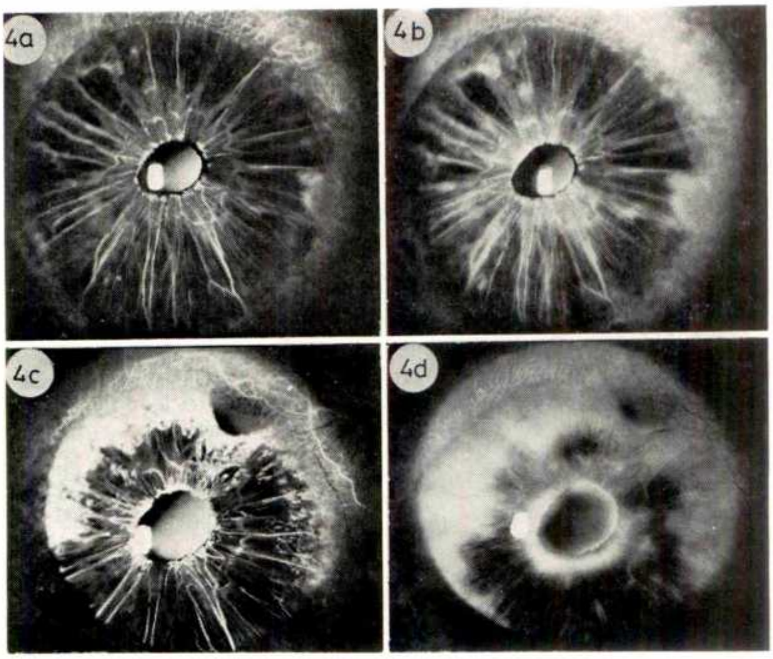

Fig. 4 (a, b) *Fluorescein angiogram of the right iris after recognition of neovascular glaucoma. Areas of peripheral neovascularisation coming from the angle* (a) *with leakage* (b). *Leakage from the radial arteries and dilated capillaries around the pupil* (b). (c–d) *Same iris 10 months later after trabeculectomy showing considerable progression of rubeosis from the angle and more dilated vessels around the pupil* (c) *with leakage* (d), *but midstromal portion almost free of neovascularisation. IOP 19 mmHg*

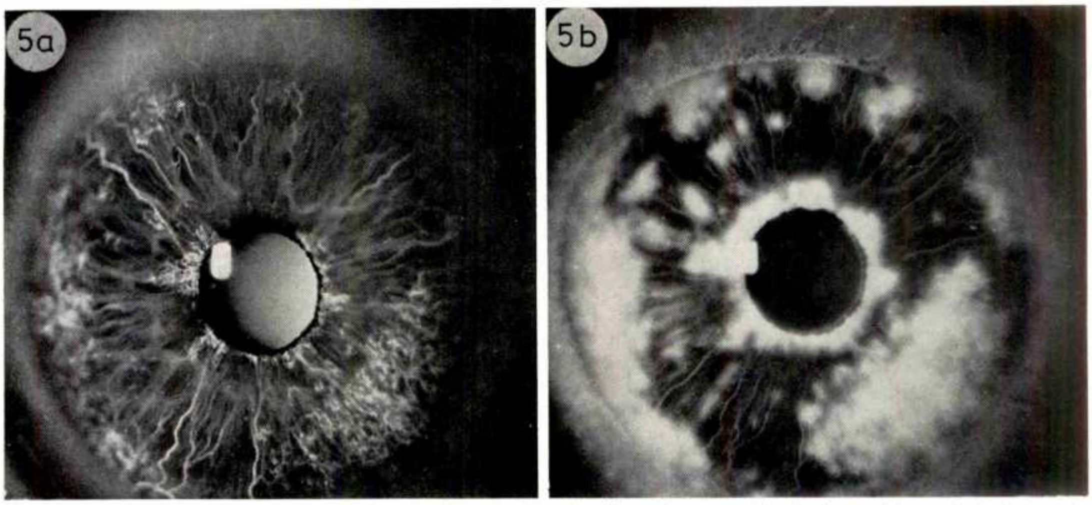

Fig. 5 (a, b) *Fluorescein angiogram of the right iris. Considerable rubeosis mainly in the periphery of the iris with profuse leakage. Mild leakage from the radial vessels*

stages of rubeosis new vessels covered the whole of the iris, the result being complete angle closure, neovascular glaucoma, and further eversion of the pigmented border of the pupil (Figs. 6*a*, *b*). There was extensive leakage from the new vessels all over the iris.

In longstanding cases new vessels were found to cross the pupillary border (Fig. 7*a*, *b*), but they were smaller in size and leaked less than in the earlier active stages of the disease.

Discussion

The first vascular abnormalities in the iris in diabetic eye disease are dilated leaking vessels around the pupil (Jensen and Lundbaek, 1968;

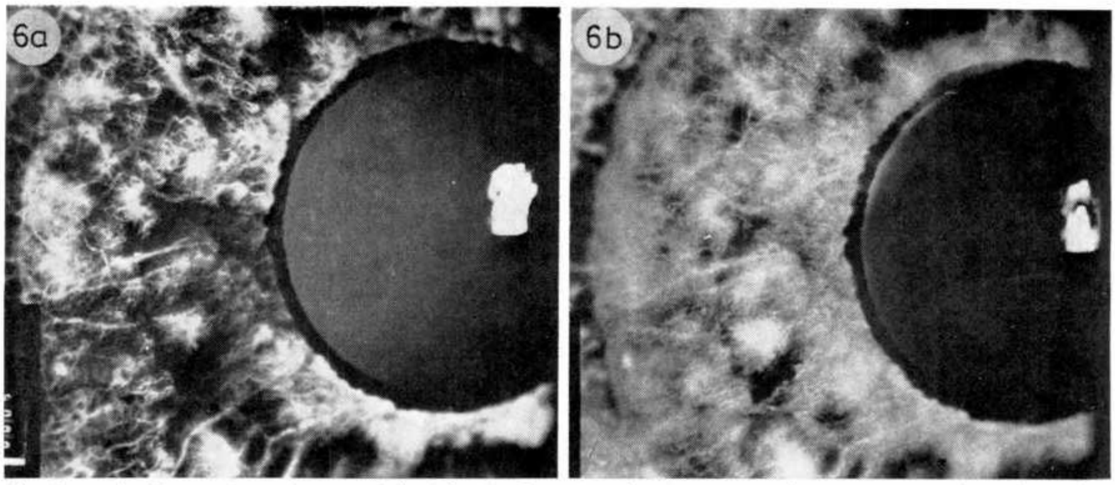

Fig. 6 (a, b) *Fluorescein angiogram of the right iris. Extensive aborising neovascularisation coming from the angle covering the whole iris* (a) *with marked leakage* (b). *IOP 40 mmHg*

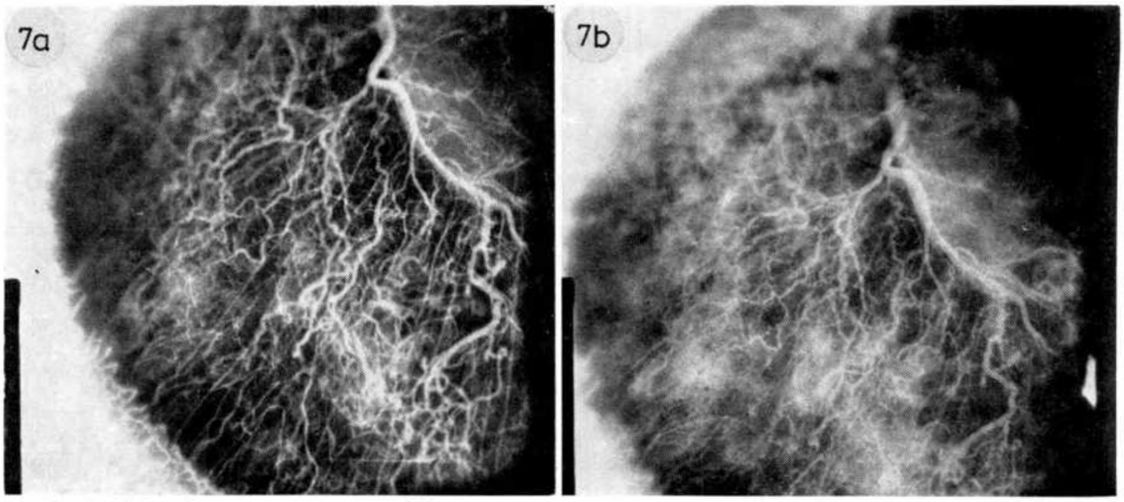

Fig. 7 (a, b) *Iris fluorescein angiogram of blind normotensive eye 19 months after iridencleisis. A large vessel trunk at the pupillary margin with branches both to the iris and the cataractous lens* (a) *with mild leakage* (b)

Baggesen, 1969; Friedburg *et al.*, 1973). In healthy eyes no fluorescein leakage is present, because the endothelial cells of the vessels of the human iris lack fenestrae and seem to be joined by tight junctions (Hogan *et al.*, 1971). Peripupillary vessel dilatations, however, are not specific for diabetes. Peripupillary vessel tufts have also been described as an isolated finding (Sellman, 1972; Israel and Lorenzetti, 1974) or in association with other diseases like myotonic dystrophy (Cobb *et al.*, 1970) or congenital cyanotic heart disease (Krarup, 1977). More generalised dilatation and leakage of the peripupillary capillaries are also commonly seen in chronic glaucoma (Vannas, 1969) and in central retinal vein occlusion (Laatikainen and Blach, 1977).

In this study it appeared that most of the early peripupillary vessel abnormalities in diabetics were dilated pre-existing capillaries that leaked fluorescein rather than newly formed vessels. Peripupillary vessel dilatations were often associated with irregular filling of the radial arteries. These changes were found to occur also in eyes with fairly mild retinopathy without significant retinal vascular occlusion. Therefore peripupillary vessel dilatations do not usually indicate an immediate danger for neovascular glaucoma, which occurs in relation to severe retinopathy.

The other vascular changes or types of neovascularisation were not specific for diabetic eye disease, for similar changes are seen associated with other vascular diseases. In the majority of eyes definite neovascularisation started in the chamber angle, and therefore newly formed vessels were usually seen earlier by gonioscopy than by fluorescein angiography. Only occasionally was neovascularisation found to spread from the pupillary border towards the periphery of the iris.

Together with new vessel formation, radial vessels, particularly arteries, started to leak fluorescein. Similar leakage has been found in the ischaemic type of central retinal vein occlusion (Vannas and Raitta, 1972; Cappin and Whitelocke, 1974; Laatikainen and Blach, 1977) and in a recent central retinal artery occlusion (Kottow, 1976), indicating the possible effect of posterior segment ischaemia on the iris. Areas of vascular closure comparable to those in the retina were not seen in the iris in any of the patients, although in some eyes filling of the radial arteries was slow. This is in contrast with the findings of Baggesen (1969), who found that the time between the appearance of fluorescence in the annulus major and at the pupillary border was shorter in diabetics with rubeosis than in non-diabetics. In eyes with high intraocular pressure or soon after a glaucoma attack leakage of the radial vessels was apparently due to local ischaemia of the iris. Similar leakage has also been described after an attack of primary angle-closure glaucoma (Vannas, 1969). Whether both posterior and anterior segment ischaemia are needed for the development of rubeosis in diabetics remains unknown.

In this series development of neovascular glaucoma was always associated with extensive and rapidly progressing retinal vascular closure. It is well known that many diabetics with retinal vascular closure and proliferative retinopathy do not, however, develop neovascular glaucoma (Madsen, 1971a). In most diabetics development of occlusive retinopathy is gradual and slow, resulting in progressive atrophy of the retina, which, it seems, does not stimulate new vessel formation as the oedematous hypoxic retina does. This might be the reason for the great difference in the incidence and rapidity of development of rubeosis and neovascular glaucoma in diabetics with proliferative retinopathy and in patients with the ischaemic type of central retinal vein occlusion. In the latter disease one-third of the eyes develop neovascular glaucoma (Laatikainen and Kohner, 1976). It is possible that a similar incidence would be found in diabetics if only the rapidly progressing cases of occlusive retinopathy were included.

Spontaneous disappearance of iris neovascularisation in diabetics has been reported (Ohrt, 1967; Madsen, 1971a, 1971b). In this study it was not seen in any of the untreated eyes. In 2 eyes panretinal photocoagulation was performed after the discovery of iris neovascularisation. In 1 eye progression of rubeosis seemed to be arrested and in the other eye rubeosis disappeared after photocoagulation, supporting the earlier observations of the favourable effect of panretinal photocoagulation on rubeosis iridis (Little *et al.*, 1976; Laatikainen, 1977).

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Value of fluorescein iridography in diagnosis of tumours of the iridociliary zone

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SUMMARY Fluorescein iridioangiography of 33 eyes with benign tumours and 22 eyes with malignant tumours is discussed. In cases of leiomyoma the tumour vessels have a distinct pattern, and fluorescence of the tumour tissue is mottled and short-lived. Malignant tumours are characterised by distortion of their vessels. Simultaneously the patches of fluorescence appear in the tissue of the tumour and lead to a diffuse confluence. Changes in the architecture of the vessels of the iris near the tumour and absence of fluorescence at the pupil margin indicate growth of the neoplasm.

At present local excision of tumours of the iris and ciliary body is commonly undertaken, but it is often difficult to be sure of the exact nature and extent of the neoplasm. The importance of fluorescein angiography in the diagnosis of choroidal tumours is well known (Sollom, 1968; Brovkina and Zinchenko, 1977), but this technique is rarely used in the diagnosis of tumours of the iris and the ciliary body. The literature on this subject is based on the examination of small groups of patients (Craandijk and Kerk, 1970; Sevel and Tobias, 1972; Wilensky and Holland, 1974; Freeman and Friedman, 1975; Brovkina *et al.*, 1977).

The results of fluorescein angiography obtained in 55 patients with tumours of the iris and iridociliary region is the subject of the present paper.

Patients and methods

Fifty-five patients (22 males and 33 females) were examined. The age of the patients ranged from 16 to 62 (mean 45·9 years). In 38 patients (69%) the tumour was situated both in the ciliary body and in the iris, in 15 (27%) in the peripheral part of the iris only, and in 2 the pupillary portion of the iris was the site of the growth.

All the patients were treated surgically. In 52 cases local excision was performed, and 3 eyes were enucleated.

Benign tumours were found in 33 cases, 30 of which were leiomyomas, 2 were naevi, and 1 was a haemangioma. Twenty-two malignant tumours were found, including melanomas in 17 eyes, epitheliomas in 2 eyes, leiomyoblastomas in 2 eyes, and a prostatic metastasis in 1 eye.

The technique of fluorescein iridoangiography has been described elsewhere (Brovkina *et al.*, 1977). 5 ml 10% sodium fluorescein is injected into the antecubital vein. By means of a photo-slit lamp SLF (Carl Zeiss, Jena) with special filters photography is performed every 2 seconds, starting 5 seconds after the introduction of the dye and continuing up to 40 seconds. A control picture is taken 40 minutes later.

Results

Leiomyoma of the iris was the most frequent finding in our material. It occurred in 30 cases of 55 (54·5%). In 7 cases the tumour was light brown or greyish brown and in 23 yellowish or pink. In 21 cases the tumour was situated in the iridociliary zone extending along the surface of the iris and producing ectopia uvea. In 8 eyes the tumour was localised to the iris root area without deforming the pupil. In 1 case a leiomyoma formed a solitary nodule at the margin of the pupil.

Angiographic findings in the eyes with leiomyoma were as follows. In 23 cases dotted staining of the tumour was observed. The dots were thought to be cross-sections of the tumour vessels, since they appeared and disappeared simultaneously with contrasting vessels of the iris.

In six eyes with non-pigmented and slightly pigmented leiomyomas a vascular network of the tumour formed a picture similar to the veins of a green leaf (Figs. 1 and 2). In 7 eyes with heavily pigmented tumours vessels were not seen. Nor were

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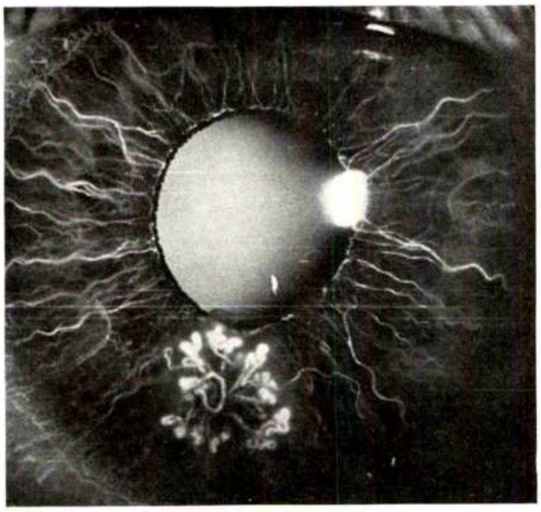

Fig. 1 *Early phase fluorescein angiogram showing the blood vessel network of a leiomyoma*

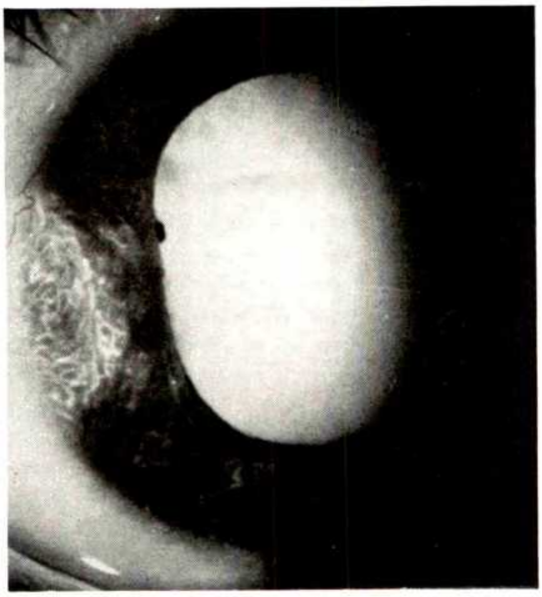

Fig. 2 *Fluorescein angiogram showing 'veins of a green leaf' pattern*

they seen in the tumour situated at the pupil margin, which resembled a jelly-like amorphous tissue through the slit lamp.

Mottled extravascular staining of the tumour was observed in 17 cases. The duration of the mottled fluorescence did not exceed 30 to 35 seconds. Not a single case of leiomyoma showed diffuse staining of the tumour tissue.

Fluorescence of the pupil margin round the whole circumference occurred in 4 cases with tumours localised to the iris root. In 23 cases fluorescence was seen only in the area of the pupil margin opposite the tumour, 16 of them showing a tumour within the iridociliary zone, 6 in the peripheral iris zone, and 1 in the pupillary zone. Complete absence of fluorescence of the pupil margin was found in 3 cases with a tumour localised in the iridociliary zone.

Second in frequency were melanomas. They occurred in 17 cases (30·9%). In 10 cases the tumour was dark brown or black, in 4 light brown, and in 3 greyish pink. In 17 eyes the tumour was clinically localised to the iridociliary area. Histologically in 10 cases the tumour extended up to the pupil margin.

Iridoangiography in 4 cases resulted in fluorescence of the vessels of the iris and tumour vessels, which in all cases were distorted, shortened, and widened (Fig. 3). At first the superficial vessels of the tumour fluoresced, the deeper vessels showing fluorescence somewhat later. On the angiograms they were presented in the shape of circular, sharply outlined dots, which seemed to be the cross-sections of the vessels. Patches of fluorescence of the tumour tissue appeared simultaneously with fluorescence of its vessels. Rapid confluence of fluorescent zones of the tumour was characteristic of these cases, which created a picture of steady diffuse fluorescence of the total surface of the tumour. This lasted up to 40 minutes when the control photograph was taken.

Four cases displayed on the angiogram rather intense fluorescence of the iris round the tumour.

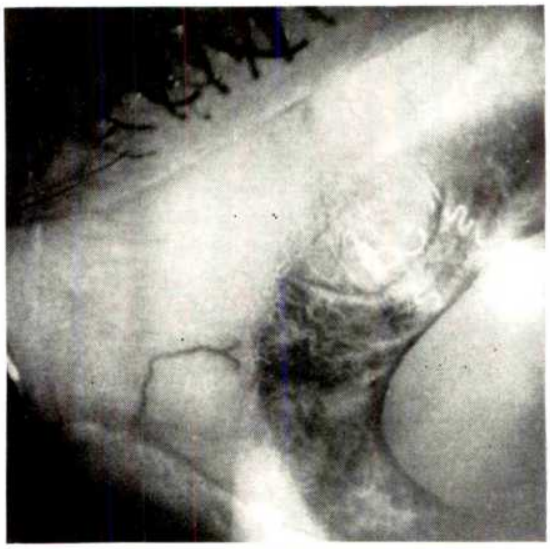

Fig. 3 *Fluorescein iridoangiogram of a melanoma of the ciliary body*

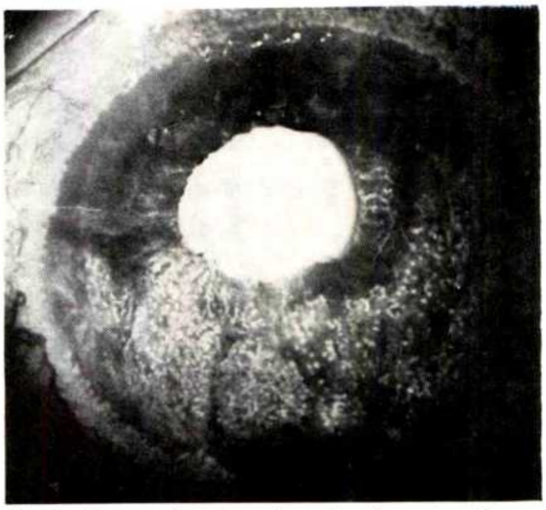

Fig. 4 *Fluorescein iridoangiography of a metastatic carcinoma of the iris*

In 12 cases noticeable changes were found in the vessels of the iris round the tumour. They showed distension and tortuosity. In 3 other cases an avascular zone in the iris round the tumour was observed. The pupil margin did not fluoresce in 14 cases.

Leiomyoblastoma occurred in 2 cases. Angiographic examination displayed fluorescence of the tumour vessels dispersed on the surface. Simultaneously there occurred mottled staining of the tumour itself, tending towards diffuse confluence. However, the fluorescence of the tumour did not last long, and it had practically disappeared by the end of the examination (40 seconds). There was no fluorescence of the pupil margin in the tumour zone.

Epithelioma of the ciliary body expanding into the iris was found in 2 eyes. In both cases the tumour was intensely pigmented, almost black. In 1 case the angiogram displayed uneven fluorescence of the iris round the tumour, which appeared after filling of the vessels of the iris with the dye.

There was 1 case of metastatic carcinoma of the iris. The tumour invaded the lower half of the iris and looked like a porous greyish mass. Iridoangiography displayed a deep change in vascular architecture of the iris, a considerable number of vessels in the tumour, with early mottled fluorescence of the tumour tissue. There was no fluorescence of the pupil margin (Fig. 4).

Haemangioma of the iris was situated in the lower temporal part of the pupil margin and looked like a pink bunch of grapes. Iridoangiography showed an unaltered net of fluorescent vessels of the iris. The pupil margin was intensely fluorescent except in the area occupied by the tumour. There was no fluorescence in the tumour.

Naevus of the iris is commoner than our material would suggest (2 eyes, 3·6% of all cases). This is accounted for by the fact that in this paper only histologically verified cases were analysed and local excision of a naevus is rarely performed. A naevus usually presented as a flat dark spot on the surface of the iris in the peripheral zone. Iridoangiography showed no changes in the vessels of the iris. The only exception was the zone of the naevus. In this zone there were no vessels or patches of pathological fluorescence. In both cases the fluorescence of the pupil margin was normal.

Discussion

Fluorescein angiography is useful in the diagnosis and differential diagnosis of tumours of the iris and the iridociliary zone. In some cases fluorescein photography shows the extent of the tumour better than other clinical methods.

One of the characteristic features of a growing tumour is the appearance of newly formed vessels which are filled with the dye at the same time as the iris vessels. In some cases cross-sections of the newly formed vessels are seen which look like circular, sharply outlined dots. In the course of the filling of the tumour vessels in leiomyomas a quarter of the cases observed produced the 'veins of a green leaf' pattern, which never presented in association with malignant tumours. In contrast, malignant tumours, especially melanomas, were characterised by a chaotic pattern of deformed vessels. The study of vessels in a tumour by angiography is feasible only in unpigmented and lightly pigmented tumours, as shown by Sevel and Tobias (1972), and Gass (1973).

Tumours are also characterised by fluorescein staining of their tissues. In cases of leiomyoma fluorescence is usually mottled, situated close to the vessels, and disappears within 40 seconds of injection of the dye. A significant feature of malignant tumours is a deeper diffuse staining. At first patches of tissue fluorescence appear. The intensity of fluorescence increases, zones of confluence then accrete and gradually diffuse staining develops across the whole tumour, which lasts for 30 to 40 minutes. This pattern is characteristic of melamoma (Amalrik and Rebiere, 1971; Wilensky and Holland, 1974; Demeler and Domarus, 1976). Rapidly developing intense fluorescence of tumour tissue suggests patency of newly formed vessels, permitting leakage of dye.

There is no fluorescence of the iris tissue in normal eyes (Harris *et al.*, 1972). The angiogram shows only the vascular network of the iris and even fluorescence of the pupil margin. In eyes with melanomas of the iris pronounced staining of the iris tissue round the tumour was seen. Expansion of the tumour leads to a disturbance of the circulation at the pupil margin, which is shown on the iridoangiogram by absence of fluorescence. In eyes with melanoma of the iris fluorescence of the pupil margin did not occur at all. In cases of leiomyoma and haemangioma fluorescence was observed only in the zone opposite the localisation of the tumour.

In all our cases fluorescein iridoangiography revealed noticeable changes in the vessels of the iris round the tumour such as displacement, distension, and tortuosity.

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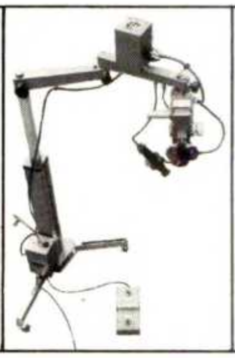

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Postinflammatory and malignant protein patterns in aqueous humour

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SUMMARY Normal aqueous humour and the aqueous humour of patients with cataract is virtually protein-free. Patients having retinoblastoma and non-malignant postinflammatory lesions show significantly high quantities of proteins in the aqueous humour. Retinoblastoma is associated with an increase in the globulin content and an albumin/globulin ratio below unity, while non-malignant postinflammatory intraocular conditions show a rise of the albumin fraction with an albumin/globulin ratio above unity. It seems likely that the leakage of protein into the aqueous is different in the two conditions, and a transcellular route is postulated as being the cause in malignant conditions. The estimation of protein patterns in the aqueous humour may be of value in the diagnosis of intraocular malignancy.

The aqueous humour in man contains identifiable concentrations of protein whose components are identical to those of plasma, showing that the proteins of the aqueous humour are derived from the blood (Esser *et al.*, 1954; François *et al.*, 1958). Though all the plasma proteins are present in the aqueous, their absolute concentrations are very low. Niedermeier (1952) gave an average figure of 13 mg/100 ml, while Kronfeld (1941) showed that the protein content of human aqueous humour varied between 5 and 16 mg/100 ml and that the amount of protein in a single sample of normal aqueous humour was between 15 and 45 μg. The concentration of protein is so small and its presence is detected with such difficulty that the aqueous humour is described as 'virtually protein-free' (Davson, 1962).

The proportions of the proteins in the aqueous differ from those in the plasma. The albumin fraction was nearly always higher, the gamma globulin fraction lower, and the albumin/globulin ratio higher in the aqueous than in the plasma (Kronfeld, 1941).

Since the discrepancy between the protein content of the aqueous and the plasma is so great, a breakdown in the blood-aqueous barrier will produce obvious effects on the protein concentration of the aqueous. It is known that after paracentesis the newly-formed aqueous is very rich in protein (Rohen, 1953). Staphylococcal infections of the eye increase the protein content of the aqueous, producing an albumin/globulin ratio of 2·3 (Sallman and Moore, 1948). Wessely (1915) showed that irritation of the cornea produced a marked hyperaemia of the intraocular vessels, which was associated with an increased protein content of the aqueous humour. Inflammatory ocular conditions and disturbances of the blood-aqueous barrier therefore increase the permeability of the ocular capillaries, enabling large molecules to pass through the blood-aqueous barrier, and the albuminous exudate so formed gives rise to a plasmoid aqueous (Duke-Elder, 1970).

Little is known about changes in the blood aqueous barrier in malignant intraocular conditions. In certain malignant tumours the capillaries are poorly supported and protein leakage is a possibility (Florey, 1970), but there is no evidence that this is so in retinoblastoma. It is known, however, that many enzymes such as lactic dehydrogenase are increased in the aqueous humour in intraocular malignancy (Dias *et al.*, 1971). Since all enzymes are proteins, the presence of excessive amounts of these enzymes in the aqueous is likely to produce an altered protein pattern in malignant conditions.

A non-inflammatory, non-malignant intraocular condition such as cataract, which is usually accompanied by a denaturation of the lens protein, is also likely to be associated with leakage of proteins through the lens capsule into the aqueous, producing a protein pattern different from that of the other two conditions.

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Table 1 *Analysis of LDH activity, total protein, and protein pattern in malignant and post-inflammatory ocular lesions*

Diagnosis	*LDH activity units/100 ml*	*Total protein (g/100 ml)*	*Protein patterns in g/100 ml*					*Total globulin*	*Albumin/globulin ratio*
			Albumin	α_1	α_2	β	γ		
1. Retinoblastoma	3650	1·4	17·9	29·9	nil	22·3	29·9	82·1	0·22
2. Retinoblastoma	2360	0·9	17·1	17·5	20·6	34·4	nil	82·5	0·20
3. Early phthisis	490	0·4	66·7	trace	trace	16·7	16·6	33·3	2·0
4. Keratomalacia	170	0·8	58·6	nil	nil	20·7	20·7	41·4	1·4
5. Adherent leucoma	350	1·8	90·8	nil	nil	9·2	nil	9·2	9·9

Little has been reported on the protein patterns in the aqueous humour in these conditions, and because the mechanisms of protein leakage and the nature of the proteins in the aqueous differ in these conditions, their protein patterns may also differ. It was therefore decided to study the protein patterns, total proteins, and the lactic dehydrogenase (LDH) activity in the aqueous humour of patients suffering from cataract and post-inflammatory and malignant lesions of the eye to determine whether differences exist in these conditions.

Materials and methods

Aqueous humour was collected by aqueous puncture from 10 patients who presented for cataract extraction at the Victoria Memorial Eye Hospital, Colombo. Two of these patients had a pseudo-exfoliation of the lens capsule, 1 had a traumatic cataract, another had a cataract with a secondary glaucoma, while the rest all had hypermature senile cataracts.

Specimens of aqueous humour were also collected from 5 patients who presented for enucleation of their eyes. Two of these had retinoblastoma, which was subsequently confirmed histologically, while the other 3 patients, whose brief case histories are given below, had non-malignant post-inflammatory intraocular disorders.

Case 3 gave a history of a piece of firewood striking the eye, and, though treated for 2 months at the Eye Hospital, Colombo, showed a shrinking eye.

Case 4 was a patient with keratomalacia with an opaque cornea who had a painful blind eye.

Case 5 gave a history of a stone striking the eye 7 months previously, which resulted in the formation of an adherent leucoma, ending up finally as a secondary glaucoma.

The aqueous humour from all these patients was analysed within 2 hours of collection for LDH activity and total protein, and its protein pattern was determined by electrophoresis.

The LDH activity was estimated by the colorimetric method of King (1959), and expressed in units per 100 ml of aqueous humour, a unit of activity being the amount of LDH which will reduce 1 μmol lactate to 1 μmol pyruvate in 15 minutes at 37°C. This method was identical to that used earlier (Dias *et al.*, 1971).

Paper electrophoresis was carried out on the samples of aqueous humour according to the method described by Wootton (1964) and the total proteins were estimated by the Biuret method.

Results

The aqueous humour from the 10 patients with cataract showed no trace of protein on electrophoresis, and the highest protein content recorded was 0·17 g/100 ml from a patient with senile cataract. The LDH activity of the aqueous humour in all these patients ranged between 140 and 360 units per 100 ml. This is within the normal limits for LDH activity in non-malignant intraocular conditions (Dias *et al.*, 1971).

The analysis of the protein patterns and the LDH activity of the 5 patients suffering from post-inflammatory and malignant lesions is shown in Table 1. The electrophoretic patterns of these patients are shown in Figs. 1 and 2.

Discussion

Although normal aqueous humour is virtually protein-free, it was thought likely that in patients with cataract with damage to the lens capsule denatured lens protein would leak into the aqueous. The above results show that even with damage to the lens capsule leakage of proteins into the aqueous is minimal, for in none of these patients could even traces of protein be detected in the aqueous on electrophoresis, and the total protein content of the aqueous was low.

Though the total protein content of the aqueous in malignant and post-inflammatory conditions is significantly higher than normal (Table 1), there appears to be no significant difference ($P=0·1$) in the total amount of protein leaking into the aqueous in post-inflammatory and malignant intraocular conditions.

Analysis of the protein patterns shows that in the 2 patients with retinoblastoma the total globulins are raised, with a corresponding lowering of the albumin fraction, while the 3 patients with non-malignant post-inflammatory eye lesions show an increase of the albumin fraction. A noticeable feature was the absence of alpha-1 and alpha-2 globulins in the aqueous humour of the 3 post-inflammatory lesions.

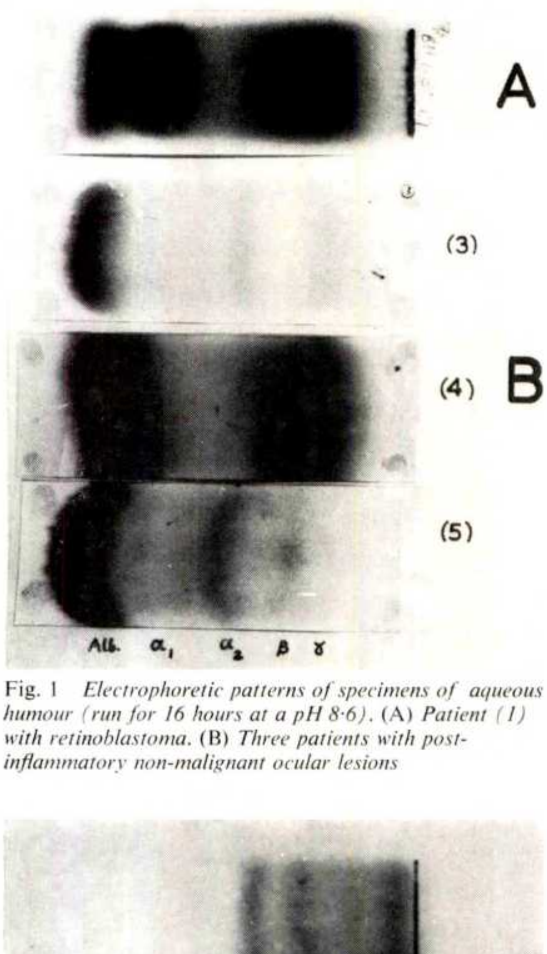

Fig. 1 *Electrophoretic patterns of specimens of aqueous humour (run for 16 hours at a pH 8·6).* (A) *Patient (1) with retinoblastoma.* (B) *Three patients with post-inflammatory non-malignant ocular lesions*

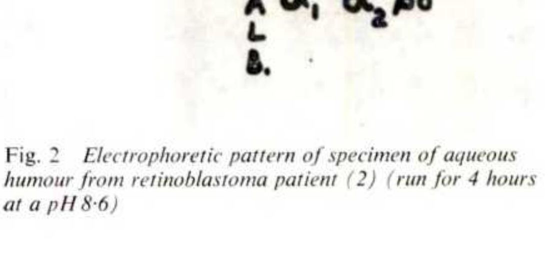

Fig. 2 *Electrophoretic pattern of specimen of aqueous humour from retinoblastoma patient (2) (run for 4 hours at a pH 8·6)*

The albumin/globulin ratio in the 2 patients with malignant lesions is below unity, while in the non-malignant conditions the ratio is above unity.

As the albumin fraction is not increased in the patients with malignant lesions, it appears likely that the mechanism of protein leakage in malignant conditions is not due to a breakdown of the blood-aqueous barrier, for, if the protein leakage was due to an increase in the permeability of the ocular capillaries, albumin would be the first protein to leak out and its concentration would be highest.

It is known that malignant cells secrete enzymes like LDH into the surrounding body fluid and that the lactic dehydrogenase activity is primarily a globulin component which does not readily exchange with the plasma constituent (Wroblewski, 1957). The globulin fraction in the aqueous humour in retinoblastoma was more than double the globulin fraction in the post-inflammatory conditions. It has also been shown that high concentrations of metabolites from the retinal nerve plexuses pass by forward diffusion through the vitreous into the aqueous humour (Dias and Amarasiri, 1978). The LDH activity of the aqueous was raised in retinoblastoma, while it was within normal limits in the post-inflammatory conditions. As the LDH activity is grossly increased in retinoblastoma, it seems likely that these enzymes and other cellular metabolic products released by malignant cells and diffusing forwards are the reasons for the increase in protein in the aqueous humour in retinoblastoma. It is postulated that the increase in protein in intraocular malignant tumours is due to a transcellular protein leak rather than a transcapillary leak.

As differences exist in the protein pattern of the aqueous humour in cataract and post-inflammatory and malignant lesions of the eye, it seems likely that the determination of the electrophoretic protein pattern in the aqueous humour might be of value in the diagnosis of intraocular malignancy.

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Primary cutaneous malignant melanoma metastatic to the iris

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SUMMARY We describe a case of cutaneous malignant melanoma metastatic to the iris as the first presenting sign of metastases 10 years after excision of the primary tumour. The histology of the excised iris metastases and the primary skin melanoma are compared. Progressive intracranial metastatic growth did not correlate with the observed regression of the residual intraocular melanoma cells during cyclical cytotoxic therapy.

Iris metastases from primary cutaneous malignant melanomas are rare, with only 4 pathologically proved cases (Wagenmann, 1900; Adamük, 1909; Font *et al.*, 1967). One case describing the response of intraocular cutaneous-melanoma metastases to cytotoxic agents has been reported (Stark *et al.*, 1971). Our case illustrates a 10-year metastasis-free interval after primary cutaneous tumour excision and then seeding only to the distribution of the internal carotid artery. The intracranial metastases progressed despite the dramatic regression of residual metastatic intraocular tumour cells in response to cytotoxic therapy.

Case report

A 26-year-old white woman presented in November 1975 with a 5-week history of blurred vision in her left eye and accompanying headaches. On examination her visual acuity was 6/4 and 6/5 in the right and left eye respectively. There was a pale, fleshy mass of 2 mm diameter in the anterior stroma of the iris superonasally in the left eye. It was situated at the collarette and slightly peaked the pupil in this quadrant. Many large pigmented cells were circulating in the anterior chamber, and similar cells were distributed in a fern-like pattern on the anterior lens capsule and on the central corneal endothelium. Applanation tonometric pressures were 17 mmHg in both eyes, and both angles were grade 4/4 on gonioscopy, with no abnormal pigmentation present. The vitreous and fundus were normal.

Physical examination revealed a skin graft on the left scapular area and no clinical evidence of metastases. Computerised axial tomography and liver and spleen scans gave normal results. Chest *x*-rays showed a left hilar mass which had not changed in size since it had first been reported 3 years previously on routine tuberculosis screening.

The patient gave a history of having had excision of a malignant melanoma of her left scapular area at the Westminster Hospital, London, 10 years previously. The tumour had been totally excised, and no metastases were found clinically or on radiological examination at that time.

In December 1975, 3 weeks after ocular examination, the iris lesion was excised through a corneoscleral limbal section nasally and a sector iridectomy. Histological examination of the excised iris lesion showed a well circumscribed malignant melanoma metastasis. Postoperatively there was an increase of pigmented cells in the anterior chamber, with visible deposition of cells on the anterior lens capsule and prominently on the lens equator nasally. Through the sector iridectomy it was now possible to see another pigmented mass adjacent to the area of lens involvement. The mass abutting the lens nasally was considered to originate probably in the ciliary body.

One month after operation chemotherapy was begun with dicarbamazine, 500 mg/day intravenously for 5 days; hydroxyurea, 2 g/day for 5 days; and BCG vaccination (Commonwealth Serum Laboratories), 75 mg/ml on days 14 and 21 of the course. Within 4 days of initiating chemotherapy the intense cellular activity in the anterior chamber and cell deposition on the lens diminished markedly to only an occasional circulating cell. The intraocular pressure, which had risen to 18 mmHg postoperatively, now dropped rapidly to 10 mmHg.

Two months after operation, however, the patient presented with a grand mal seizure. Cellular activity

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in the anterior chamber was again much increased. Dynamic and static brain scans, computerised axial tomography, and electroencephalogram were within normal limits. The hilar mass remained unchanged. Once again she was given a course of cytotoxic agents like the previous one, and within 4 days the cellular activity in the anterior chamber again diminished to an occasional circulating cell. Her vision could be corrected to 6/9 in the left eye, and the intraocular pressure was 12 mmHg.

Three months after operation a third course of cyclical combined chemotherapy with dicarbamazine and hydroxyurea and BCG was begun. Within 5 days the cellular activity in the anterior chamber, which had slowly increased over the preceding month, dramatically abated. At this time her vision was 6/6, and her intraocular pressure was 25 mmHg. The increased pressure was unresponsive to acetazolamide, and gonioscopy showed a heavily pigmented angle with cells similar to those circulating in the anterior chamber and deposited on the lens capsule.

Four months after operation the patient was admitted to hospital with mental confusion, headaches, and vomiting. A brain scan showed probable secondary deposits of melanoma. Despite steroid therapy her condition deteriorated, and she died 5 days after admission. Necropsy revealed multiple intracranial melanotic deposits but no other evidence of extraocular metastasis. Permission for ocular enucleation was refused by the family.

Discussion

Ocular metastasis from primary cutaneous malignant melanoma is uncommon, with 33 pathologically proved cases reported (Landesberg, 1869; Brömser, 1870; Schiess-Gemuseus and Roth, 1879; Pflüger, 1885; Wagenmann, 1900; Jensen, 1906; Adamük, 1909; Uhler, 1914; Ten Doesschate, 1921; Boente, 1929; Cordes and Horner, 1930; Corrado, 1931; Fry, 1933; Kreibig, 1935; Wilder, 1946; Jensen, 1957; Liddicoat *et al.*, 1959; Riffenburgh, 1961; Covell and Markiewitz, 1961; Das Gupta and Brasfield, 1964; Font *et al.*, 1967; Szeps and Patterson, 1969; Stark *et al.*, 1971; Ferry, 1972; Günther, 1973; Kremlicka *et al.*, 1974; Fishman *et al.*, 1976). Only 5 of those cases showed iris involvement (Wagenmann, 1900; Adamük, 1909; Font *et al.*, 1967; Stark *et al.*, 1971). Intraocular metastases were most commonly to the choroid.

The present case illustrates one of the few clinical situations where excisional biopsy of a solitary iris nodule is indicated for diagnostic purposes. The diagnosis of this iris nodule as a first manifestation of malignant melanoma metastases 10 years after the primary excision, together with negative brain, lung, and bone scans, was unexpected. The possibility that the nodule was either a primary melanoma of the iris or a secondary deposit from another occult neoplasm had to be considered. The early diagnosis of metastasis from cutaneous malignant melanoma or from another occult primary neoplasm was essential for treatment. Because of its accessible location the nodule was excised by a sector iridectomy, with histological proof of excision beyond the tumour margin. The histological report defined the nodule as showing a thickening of the iris stroma by a malignant melanoma near the pupil. The growth was not encapsulated, but it was reasonably well circumscribed and appeared to have been totally removed surgically. The malignant cells, which were of epithelioid type, were strikingly uniform in size and configuration and were grouped in conspicuous acini (Figs. 1 and 2). A few of the

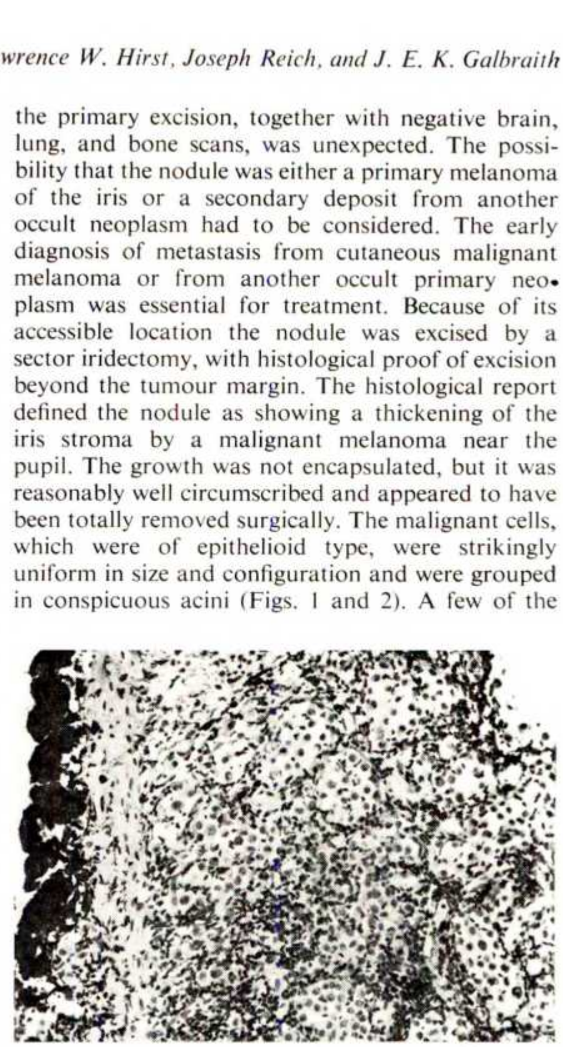

Fig. 1 *Part of iris metastasis showing round-cell infiltrate and alveolar formation of epithelioid melanocytes in the iris stroma. H. and E., × 85*

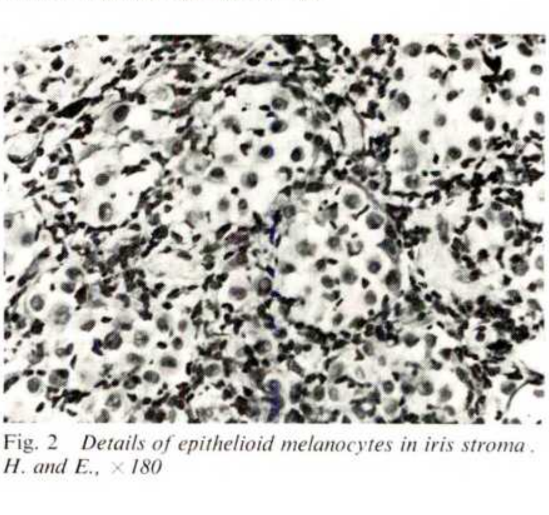

Fig. 2 *Details of epithelioid melanocytes in iris stroma. H. and E., × 180*

cells contained melanin in the form of fine granules. The uniformly epithelioid character of the cells throughout the growth, in conjunction with the clinical features of the case, was strongly in favour of a metastatic malignant melanoma.

Re-examination of the primary cutaneous tumour sections showed melanoma cells of epithelioid type, arranged in alveoli at the dermal-epidermal junction. Nests of epithelioid melanocytes were seen separated by fine fibrous septa, and there was some streaming of melanocytes into the dermis.

Examination of this primary tumour showed the margins to be free of tumour tissue and with no evidence of local extension. The cell type and cell arrangement in the primary and secondary tumours were similar. Although the possibility that this iris nodule was a primary iris melanoma cannot be ruled out, the presence of cerebral melanoma metastases at necropsy within months of the emergence of the iris lesion strongly suggests that cutaneous malignant melanoma was the source of all the melanoma deposits.

Intraocular tumours, whether primary or metastatic, that simulate iridocyclitis have been well described (Zimmerman 1968). In the present case after the sector iridectomy a probable ciliary-body metastasis was visualised and it continued to shed cells into the anterior chamber with deposition in the angle and on the anterior lens capsule. The dramatic decrease in cellular activity in the anterior chamber within 4 days of beginning 3 consecutive courses of chemotherapy was achieved without any topical administration of drugs. This may represent the earliest documented *in-vivo* response of malignant melanoma metastases to chemotherapy. This apparent responsiveness of the metastases to the combined chemotherapy supports previous reports that systemic cytotoxic agents are effective against intraocular melanoma metastases (Stark *et al.*, 1971).

It is probable that the intraocular and intracranial metastases occurred simultaneously even though initial computerised axial tomography of the brain was negative. An intracranial nodule of similar size to the 2 mm-diameter iris mass would have been well below tomography resolution threshold. However, apparent response to cytotoxic therapy of the residual exfoliated melanoma cells in the eye was not paralleled by involution of the intracranial metastases, which continued to enlarge. This paradox can perhaps be explained by many factors—including the level of local drug distribution in the tissues, metastatic cellular cohesion properties, and the tumour mass.

Metastasis of malignant melanoma from the skin to the central nervous system exclusively is rare (Pennington and Milton, 1975). Intracranial metastases from the skin would suggest spread via the internal carotid system, which explains also the intraocular involvement. The location of the intraocular metastases in the iris would also indicate direct arterial embolisation, as shown by tumour seeding experiments that show preferential anterior-segment involvement (Albert *et al.*, 1967). This, however, is in contrast to the majority of actual intraocular sites of metastases in necropsy findings (Ferry and Font, 1974).

The rapid deterioration in the patient's clinical condition after the appearance of the first metastasis is consistent with the known behaviour of intracranial malignant melanoma metastases (Pennington and Milton, 1975).

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Thyroid carcinoma metastatic to the globe

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SUMMARY We report a case of thyroid carcinoma metastatic to the globe. In our survey we found thyroid carcinomas to metastasise to the eye rarely. In addition, we found metastases from the thyroid to be more common to the orbit than to the globe—a reverse of the pattern noted with tumours in general.

Recently we had the opportunity to evaluate a patient in whom we found a metastatic lesion in the globe from a primary thyroid carcinoma. This led us to review the literature for a survey of the incidence of metastatic thyroid carcinoma to the globe. We found such metastasis to the globe distinctly rare.

Case report

A 57-year-old black woman was diagnosed as having follicular carcinoma of the thyroid in 1969. The tumour was apparently totally excised at that time. The patient had been previously healthy except for the onset of a left Bell's palsy in 1967 and a long history of neurosensory hearing loss. After the excision of her thyroid carcinoma the patient was maintained on L-triiodothyronine, 50 mg 4 times a day. In June 1973 a nodule was noted in the right paratracheal area which was subsequently shown to be positive for ^{131}I uptake. A therapeutic dose of 150 mCi of ^{131}I was administered at that time and L-triiodothyronine was again reinstituted. In May 1974, the patient was found to have a left paratracheal lesion positive for ^{131}I uptake, which subsequent biopsy showed to be metastatic follicular carcinoma of the thyroid. The patient again received 150 mCi of ^{131}I.

In November 1974 the patient reported the onset of radicular pain in her lumbosacral area. ^{131}I-scanning of the lesion was positive, and a biopsy result compatible with metastatic follicular carcinoma prompted local radiation therapy (5500 rads). In June 1975 an opacity in the left lung was noted on chest *x*-ray to be consistent with another metastatic thyroid lesion, and the patient was treated with doxorubicin hydrochloride (Adriamycin) 80 mg/m^2 for 3 weeks.

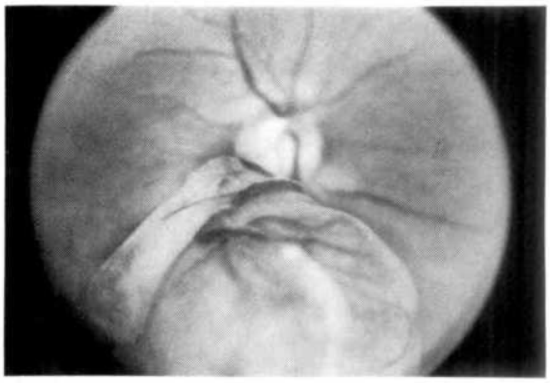

Fig. 1 *Large solid lesion in the right fundus, extending into the vitreous*

The patient was first seen at our eye clinic in August 1976 with the chief complaint of dyschromatopsia of the right eye. Past eye history was negative except for a brief bout of bilateral iritis that had resolved in 1973 after treatment with topical steroids and atropine.

In August 1976 the best corrected vision was found to be 20/60 in the right eye and 20/30 in the left eye. The extraocular movements and pupillary reactions were normal. There was no exophthalmos, and nothing abnormal was found on palpating the orbit. Examination of the lids, lashes, conjunctiva, and sclera showed nothing abnormal. Crenated keratic precipitates of both corneas were noted, but the anterior chamber, iris, and lens in both eyes were normal.

Funduscopy of the right eye revealed a large, pink lesion of solid appearance extending from the inferior border of the disc to the inferior equatorial region (Fig. 1). Funduscopy of the left eye was unremarkable.

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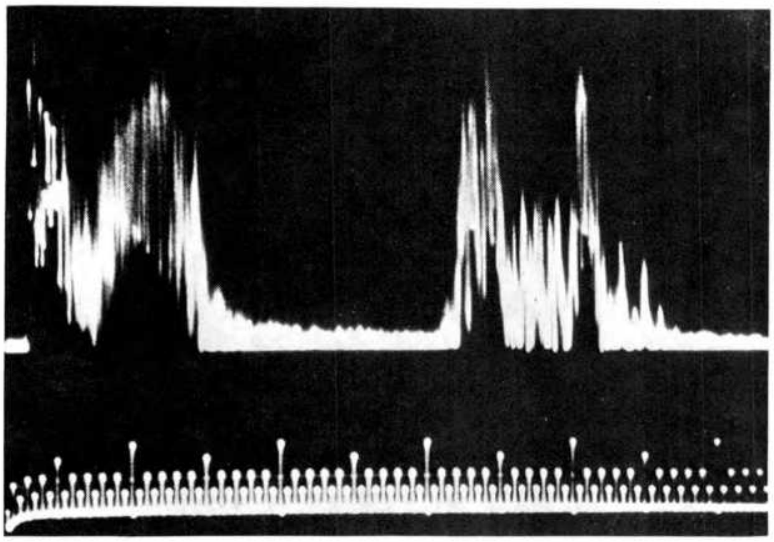

Fig. 2 *A-scan of right eye showing a solid, posterior lesion of approximately 9 mm height*

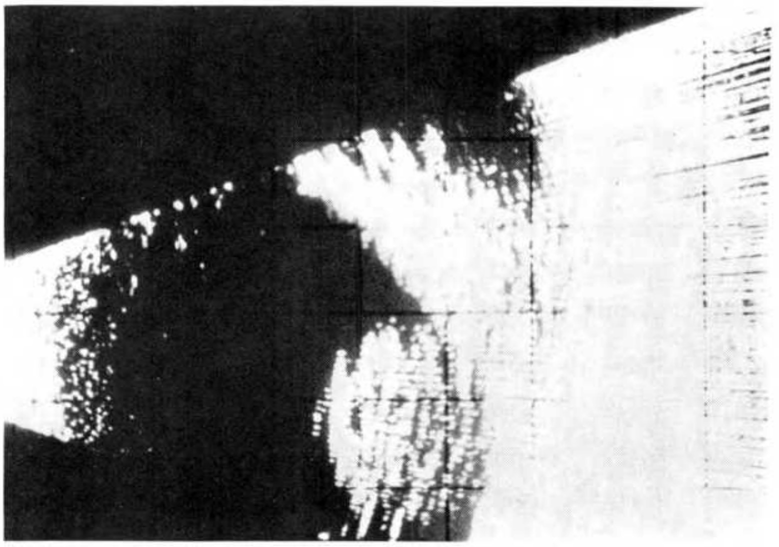

Fig. 3 *B-scan of right eye showing a round, elevated, solid, posterior intraocular lesion*

Examination of the visual field of the right eye showed a depression of the superior field with steep borders extending to include fixation. A- and B-scan of the right eye and orbit (Figs. 2 and 3) were compatible with a solid, elevated posterior pole lesion involving the posterior wall of the globe but not the orbit. Fluorescein angiography of the same lesion (Fig. 4) showed 2 contiguous choroidal lesions that leaked fluorescein profusely. An ^{131}I-scan of both orbits and of the paratracheal area was performed and was negative. The patient, however, had inadvertently continued to take her L-triiodothyronine prior to the scan. After discontinuation of the medication a repeat scan was positive for ^{131}I uptake in the right orbital area and, in addition, in 3 distinct areas in the thyroid bed (Fig. 5).

The patient's vision in the right eye over the following week was reduced to hand motion secondary to a spontaneous vitreous haemorrhage. She was treated with 4985 rads from a cobalt-60 unit to the right orbital and periorbital area through a single right lateral port. Over the following 6 months there was a clearing of the vitreous haemorrhage, but the patient developed a total retinal detachment.

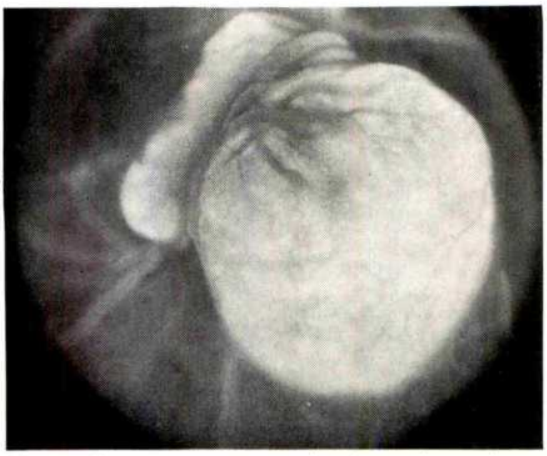

Fig. 4 *Fluorescein angiogram of right eye showing heavy fluorescein concentration in the lesion*

There was no evidence of progression or regression of the tumour. The visual acuity in the right eye 12 months after radiation therapy was light perception.

Discussion

The orbit and globe are not in the list of common sites to which systemic carcinoma metastasises. Reports of incidence vary. Hart (1962) and Rose (1965) point out that metastases to the globe and orbit are relatively infrequent. A survey (Albert *et al.*, 1967) of 213 patients with primary tumours disclosed 10 patients who had eye or orbital metastases—an incidence of 4·7%, which the authors thought suggested more frequent metastasis than previously shown. Bloch and Gartner (1971) studied 230 patients with known systemic carcinoma regardless of clinical evidence of orbital or ocular involvement and found 28 eyes with eye/orbital metastases—a 12% incidence. There is general agreement that among primary malignancies the ones most commonly found to metastasise to the eye or orbit are from the breast and lung (Hart, 1962; Jensen, 1970; Bloch and Gartner, 1971; Font and Ferry, 1976). Other less frequent primaries found to do so are in the kidneys, testicles, prostate, and bowel (Hart, 1962; Jensen, 1970; Bloch and Gartner, 1971; Ferry and Font, 1974, 1975; Font and Ferry, 1976). In our survey we specifically looked for reports of ocular metastasis from the thyroid.

Evaluation of orbital and ocular metastases can be approached in several ways. The authors in 2 surveys (Albert *et al.*, 1967; Bloch and Gartner, 1971) looked at metastases of systemic carcinomas. In combining their data we found among 443 cases 9 to be primary thyroid tumours; of these only 1 case was found to have ocular/orbital metastasis (it was unclear whether to the globe or orbit).

Two studies surveyed the sites to which primary carcinomas of the thyroid metastasise. Heitz *et al.* (1976) studied 573 primary malignant thyroid tumours and list none as metastatic to the eye or orbit. Frazell and Duffy (1951) studied 40 cases of Hürthle cell cancer of the thyroid and found 1 of these to be metastatic to the eye, but it was unclear whether to the eye or orbit.

In evaluating eye and orbital metastases Hart (1962), among 133 cases from the Armed Forces Institute of Pathology, found 1 to be of thyroid origin with metastasis to the uvea. Ferry and Font (1974) several years later analysed 227 Armed Forces Institute of Pathology cases and again listed 1 case of thyroid carcinoma metastasising to the uvea.

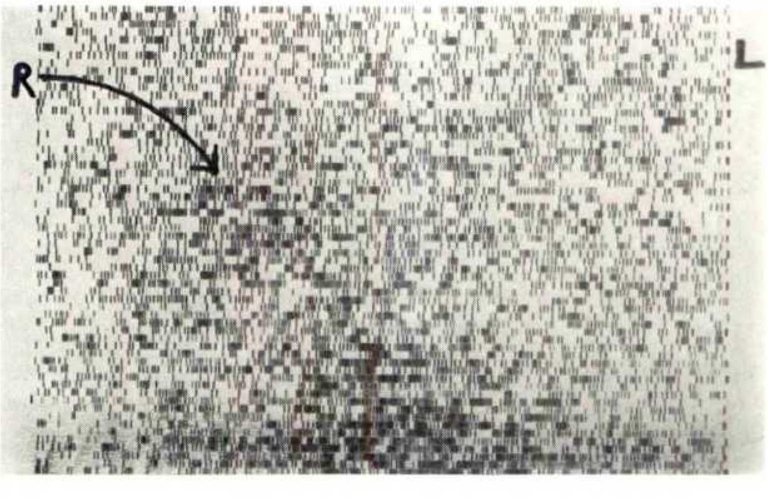

Fig. 5 ^{131}I *scan interpreted as showing significant uptake of* ^{131}I *in the right orbit and in the thyroid bed*

Presumably this case is the same one alluded to 9 years earlier by Hart.

Among 51 orbital tumours Rose (1965) found 5 to be metastatic from the thyroid. In every instance the thyroid metastases were to the extraocular muscles.

In addition to the larger series already mentioned we found 4 other reports (Knapp, 1923; Appalanarsayya and Satyrendran, 1964; Oberman *et al.*, 1969; Dhoine *et al.*, 1973), each one dealing with 1 case of thyroid metastasis. In each instance the metastasis involved the orbit.

Finally, 2 standard textbooks (Henderson, 1973; Reese, 1976) mention thyroid metastases to the eye. Henderson (1973) describes 2 cases of thyroid carcinoma both with metastases to the orbit. Reese (1976) alludes to thyroid metastasis to the eye under subheadings of uveal, eyelid, and orbital metastases. He shows fundus pictures of the posterior pole of a case of metastatic thyroid carcinoma to the choroid of both eyes.

In short, in addition to our present report our review reveals a total of 15 primary thyroid carcinomas metastatic to the eye or orbit. In 2 cases the exact location is not specified clearly. It is noteworthy that 11 of the 15 cases are definitely orbital metastases and only 2 are definitely ocular. The reason for such a propensity is unclear. It is known that both follicular and papillary carcinoma of the thyroid can spread to lymph nodes (Williams, 1974). Duke-Elder and Wybar (1961) state: 'In the orbit there are no lymphatic nodes and no lymphatic vessels have been demonstrated.... Probably the main lymph drainage from the orbit accompanies the veins through the inferior orbital fissure to the internal maxillary nodes; thence to the superior deep cervical nodes.' A study using radioisotope thyroidolymphography and orbitolymphography (Kriss, 1970) suggests a probable lymphatic channel connection between the thyroid gland and the orbit. Konishi *et al.* (1974) consider that such thyroido-orbital lymphatic channel anastomoses may be the route for orbital deposition of thyroglobulin-antithyroglobulin immune complexes with Graves's ophthalmopathy.

The apparent predisposition of thyroid carcinoma to orbital rather than ocular spread could be compatible with Kriss's (1970) proposed thyroido-orbital pathway, but may well occur on a still unexplained basis. It is, nevertheless, interesting that in animal experiments (Albert *et al.*, 1967) as well as in clinicopathologic studies (Bloch and Gartner, 1971; Ferry and Font, 1974) it appears that tumours in general seem to metastasise to the eye itself in most instances. In our review it seems that with thyroid carcinoma the pattern is reversed: thyroid carcinoma metastases to the orbit are commoner than to the globe.

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Epipalpebral conjunctival osseous choristoma

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SUMMARY Two cases of osseous choristoma are described. One of the tumours was found in the conjunctiva of the right lower lid, an apparently unique location. The other more typical epibulbar tumour was found in the superior temporal quadrant of the episclera between the lateral and superior rectus muscles. In both instances the tumour was suspected of being a dermoid.

Osseous choristomas are rare lesions of the conjunctiva, episclera, and choroid. They usually are described as a pea-to-almond size nodule of compact bone surrounded by a connective tissue capsule. They appear mainly in the superior temporal quadrant of the episclera, between the lateral and superior rectus muscles. There have been at least 38 cases of epibulbar and 5 cases of choroidal osseous choristomas described (von Gräfe, 1863; Spencer-Watson, 1871; Saemisch, 1876; de Wecker and Landolt, 1880; Critchett, 1882; Walker, 1882; Loring, 1883; Snell, 1884; Vignes, 1889; Wagenmann, 1889; Cirincione, 1895; Galtier, 1895; Hartridge, 1895; Nettleship, 1895; Heustis, 1899; Parsons, 1904; Collins, 1927; Ballantyne, 1940; Boniuk and Zimmerman, 1962; Delmotte *et al.*, 1962; Wiesinger and Guerry, 1962; Beckman and Sugar, 1964; Sihota, 1964; Kaufer and Plater, 1968; Roch and Milauskas, 1968; Kreibig and Nehm, 1969; Ferry and Hein, 1970; Fanta, 1977; Gass *et al.*, 1978). None of the previously reported cases involved the lower lid.

Case reports

CASE 1

A 13-year-old boy was noted by his mother to have 'tissue resembling a scar' over the conjunctiva of his right eye. Ophthalmological examination revealed a 5×5 mm lesion in the superior temporal quadrant of the right globe between the lateral and superior rectus muscles (Figs. 1 and 2). The remainder of the ocular examination showed no abnormalities. The clinical diagnosis was dermoid, right eye.

Macroscopically the specimen consisted of a hard lenticular fragment of tissue measuring 4×3×2 mm. Microscopically a fragment of bone surrounded by collagenous connective tissue was noted (Fig. 3).

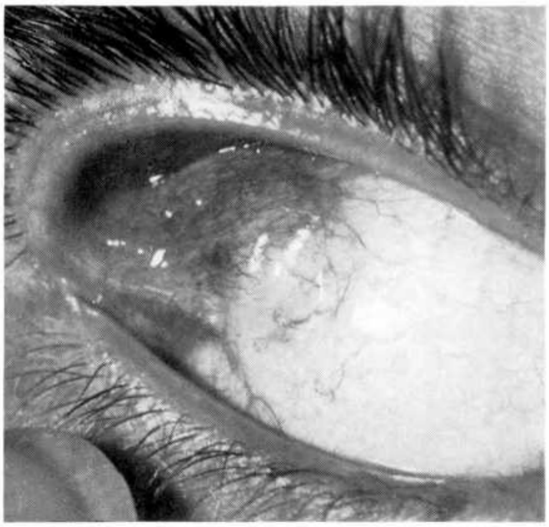

Fig. 1 *Case 1. The superior temporal quadrant reveals a raised lesion*

CASE 2

An 8-month-old girl had a lesion protruding from the temporal side of the conjunctiva of her right lower lid; there was no connection to the bulb. The lesion was first noted at the age of 6 weeks. At that time the child was brought to the ophthalmologist because of increased tearing of the right eye. The clinical diagnosis was dermoid of the right lower lid. Over the next 6 months the child had progressive mucopurulent discharge from both eyes which seemed to be secondary to obstructed nasolacrimal ducts. The lesion in her right lower lid was thought to have enlarged slightly and was removed. At the

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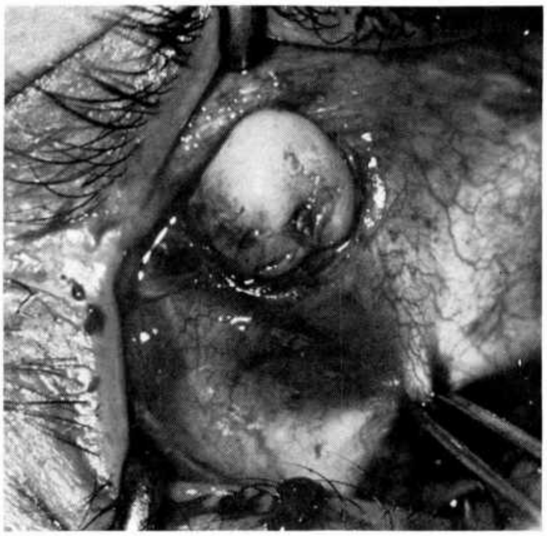

Fig. 2 *Case 2. At surgery a 4 × 3 × 2 mm oval-shaped osteoma was excised*

time of surgery the lesion was diagnosed as pyogenic granuloma. The dacryostenosis was relieved by probing and irrigation.

Macroscopically the specimen consisted of an 8 × 3 × 1 mm fragment of hard, white, nodular tissue. Microscopically a spicule of bone with haemopoietic marrow was noted (Fig. 4).

Discussion

There have been scattered reports of unusual appearances of osseous choristomas. Roch and Milauskas (1968) had 2 cases of epibulbar osseous choristoma which extended to the lateral rectus muscle sheath. A similar finding was also described by Ferry and Hein (1970). Fanta (1977) noted an osseous choristoma arising from the outer canthus of the left eye with no connection to the bulb. Gass *et al.* (1978) described 5 cases of choroidal osseous choristomas, 1 of which was confirmed by histopathology. Although also characteristically occurring in young women, the relationship of these intraocular tumours to lesions of the episclera is not clear.

In the 43 reported cases, as in the ones described here, the superior temporal epibulbar location of the osseous choristoma was cited in 23 (51 %) of the cases. The temporal epibulbar location was described in 14 (31 %) of the cases; the exact site was not listed in 2 (4 %). Choroidal osseous choristomas were found in 5 (11 %) of the cases. No report could be found where the lower lid was involved.

The majority of epibulbar tumours are discovered and excised by the time the patient is 14 years of age. They have been found to be twice as common in females.

In our Case 1 the lesion was found in the temporal outer quadrant of the episclera in an adolescent. This location is the same as in the majority of cases of epibulbar osseous choristomas. In our Case 2 the lesion was found in the temporal side of the conjunctiva of the right lower lid, in a child with bilateral dacryostenosis. The question is raised here of the possibility that the tumour may have been related to chronic inflammation. Galtier (1895), Boniuk and Zimmerman (1962), and Roch and Milauskas (1968) list several cases in which patients had a history of trauma preceding the appearance

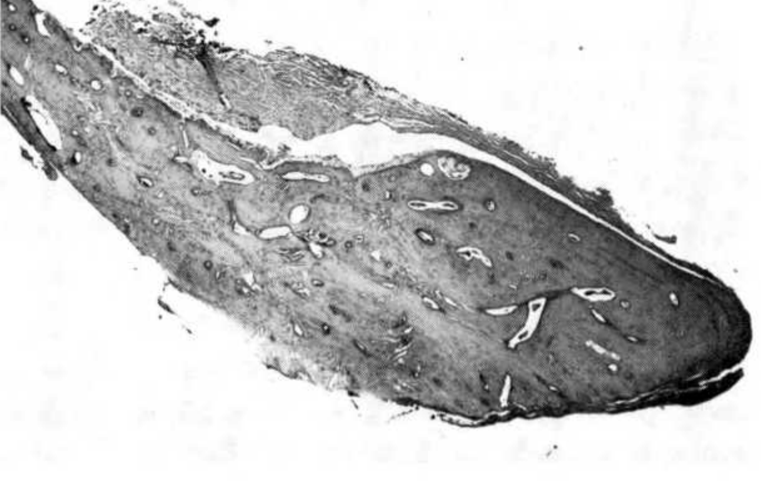

Fig. 3 *Case 1. Bone encapsulated in a connective tissue capsule (H and E × 10)*

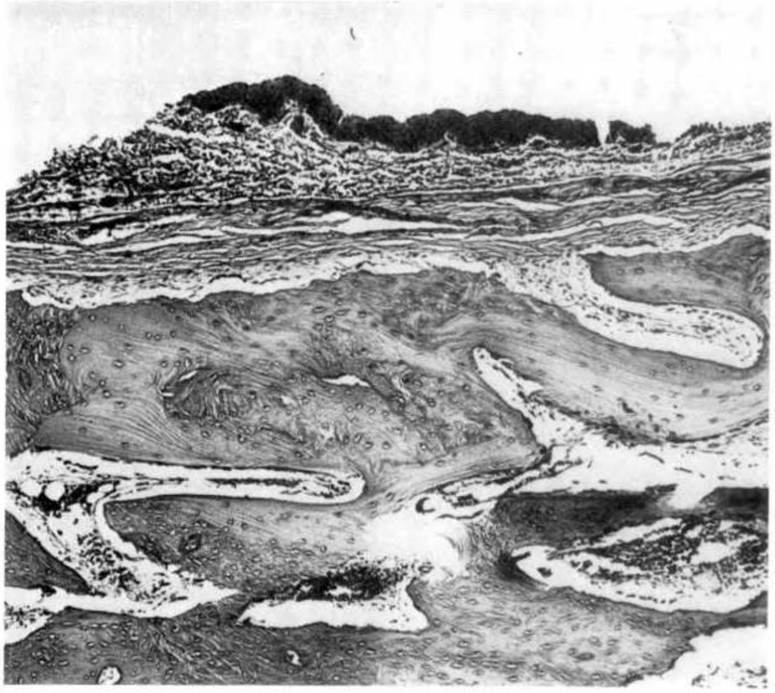

Fig. 4 *Case 2. Zones of haemopoietic marrow are seen in the fragment of bone (H and E × 12)*

of the osseous choristoma. Boniuk and Zimmerman (1962) speculated that the trauma may have alerted the patient to an already pre-existing lesion. Other causes proposed (in addition to congenital, inflammatory, and traumatic) include atavistic remnant (Boniuk and Zimmerman, 1962; Roch and Milauskas, 1968) and embryonic rest of the mesodermal layer (Roch and Milauskas, 1968). Collins (1927) thought that the lesion could be a result of embryological metaplasia. Because most of the tumours are discovered in infancy and are usually located between the lateral and superior rectus muscles, the congenital cause seems the most plausible.

Epibulbar osseous choristomas are often confused clinically with epibulbar dermoids. Boniuk and Zimmerman (1962) elucidated the essential differences between the two lesions: (1) Epibulbar osseous choristomas are composed entirely of compact bone whereas epibulbar dermoids are composed of associated dermoid structures; (2) epibulbar dermoids are usually located in the inferior temporal rather than the superior temporal quadrant of the globe; and (3) epibulbar dermoids are frequently (30%) associated with congenital anomalies, usually involving malformations of the branchial arch derivatives (Crawford, 1976), whereas epibulbar osseous choristomas are thought to be a result of the above-described causes.

Beckman and Sugar (1964) noted that a simple preoperative *x*-ray examination of a suspected lesion would detail the radio-opacity of the osseous choristoma and help in the differential diagnosis of osseous choristoma from radiolucent dermolipomas and epibulbar dermoids. Two cases of epibulbar dermoids associated with bone have been reported, but they are isolated cases (Wagenmann, 1889; Ferry and Hein, 1970).

In previous reports these bony tumours have been termed epibulbar osteoma (Ballantyne, 1940; Sihota, 1964; Roch and Milauskas, 1968), episcleral osseous choristoma (Boniuk and Zimmerman, 1962), epibulbar osseous choristoma (Beckman and Sugar, 1964; Ferry and Hein, 1970), and choroidal osteoma (Gass *et al.*, 1978). But, as seen in our second case, the tumour can also be found in the conjunctiva of the lower lid. Although it is a minor point, we consider that epipalpebral conjunctival osseous choristoma is a proper term for this variety of osseous choristoma, since it defines the exact location of the lesion and emphasises its non-attachment to the bulb.

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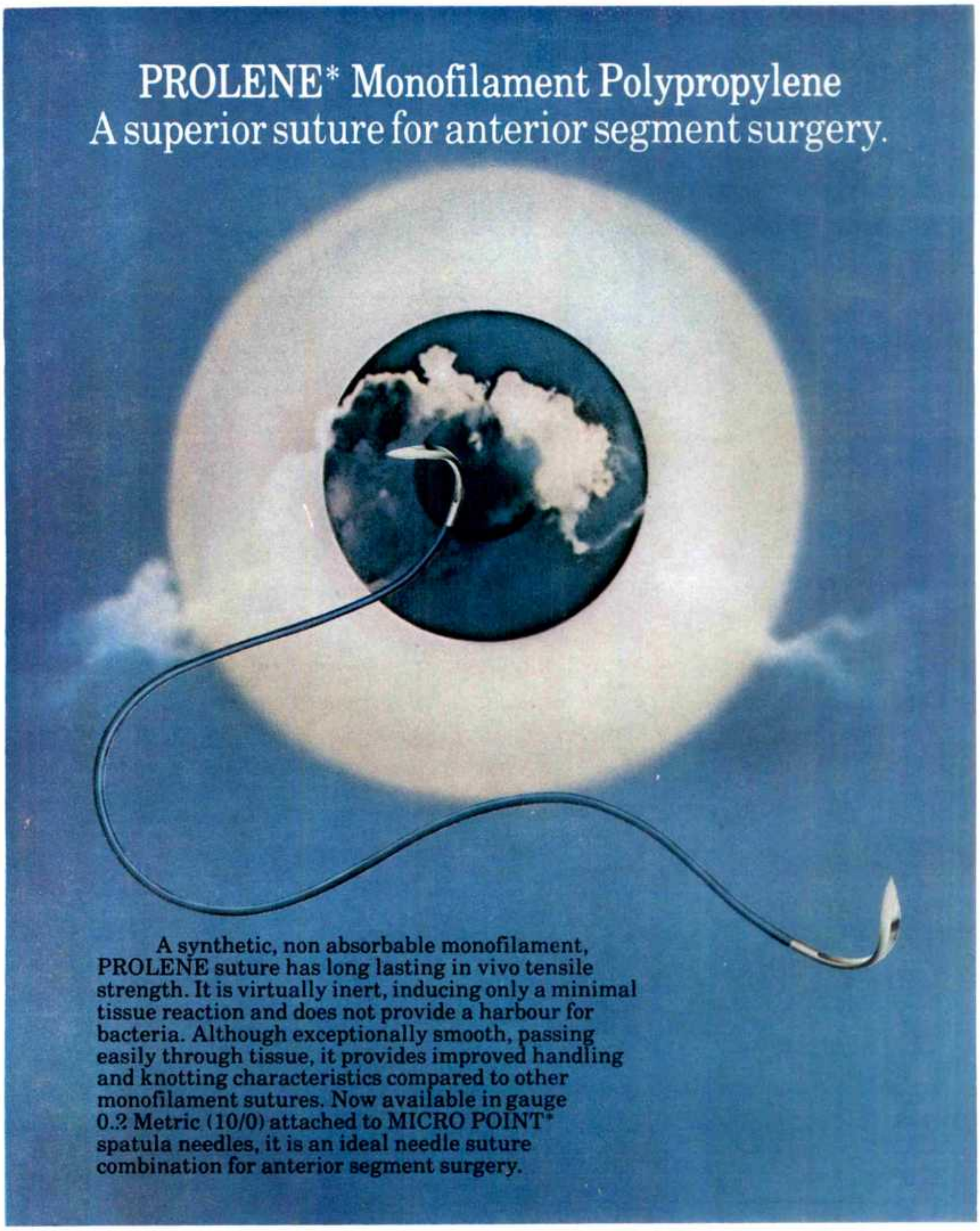

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Scleral and choroidal calcifications in a patient with pseudohypoparathyroidism

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SUMMARY This case report suggests that calcifications in the sclera and choroid may be a feature of pseudohypoparathyroidism and shows a calcium distribution more extensive and severe than that characteristically seen in other metabolic conditions associated with calcium deposits in the eye. Ocular ectopic calcification is a part of the more generalised ectopic soft tissue calcification seen with pseudohypoparathyroidism. Evaluation of the contribution of the terminal renal failure and uraemia to the ectopic ocular calcification would require sequential evaluation of eyes with pseudohypoparathyroidism, but without the added complication of uraemia.

Calcification of the sclera and the choroid associated with pseudohypoparathroidism has not been previously reported. This paper describes a patient in whom this condition apparently contributed to such calcification. Other causes of calcification in the sclera and choroid are reviewed.

Case report

Our patient was a white female dietary worker who died in 1977 at 29 years of age from complications of pseudohypoparathyroidism. She was diagnosed to have this disorder at the Massachusetts General Hospital in 1956 at the age of 9 years. Pseudohypoparathyroidism was initially suspected because of the characteristic habitus of truncal obesity, round facies, shortening of the fourth metatarsals, recurrent subcutaneous calcifications in the extremities, mental retardation with an IQ of 67, and biochemical abnormalities of hypocalcaemia (7·2 mg/100 ml (1·8 mmol/l); normal 9·0 to 11·5 mg/100 ml (2·25 to 2·87 mmol/l)), and hyperphosphataemia (9·7 mg/100 ml (3·13 mmol/l); normal 3·0 to 4·5 mg/100 ml (0·97 to 1·45 mmol/l)). No eye abnormalities were noted on examination at that time. At the time of her diagnosis the patient was begun on supplemental vitamin D of 50 000 units per day. While she was on this regimen her serum calcium levels were found to be in the range of 8 to 10 mg/100 ml (2 to 2·5 mmol/l), while her serum phosphate levels were reported in the range of 6·8 to 9·5 mg/100 ml (2·20 to 3·07 mmol/l).

The vitamin D therapy was discontinued in 1963. The patient did well for 2 years, but in 1965, at the age of 17, she developed grand mal seizures. The results of hospital studies carried out at that time revealed a serum calcium level of 5·6 mg/100 ml (1·4 mmol/l), a skull *x*-ray indicating calcification in the caudate nuclei, and an electroencephalogram (EEG) suggestive of 'structural brain disease'. Her seizures were attributed to her hypocalcaemic state, and vitamin D was administered at a dose of 100 000 units per day. In addition she was given supplemental calcium (calcium chloride 30% in 5-ml doses by mouth 3 times a day) and phenytoin sodium 100 mg by mouth twice a day.

In 1968, while maintained on 100 000 units of vitamin D per day, the patient developed symptoms which were suggestive of vitamin D intoxication. She had bleeding from the upper gastrointestinal tract and a serum calcium of 13·5 mg/100 ml (3·37 mmol/l). Her vitamin D was discontinued, and her serum calcium levels declined to normal limits. At that point vitamin D therapy was begun at a reduced dose of 50 000 units per day. During her hypercalcaemic state the patient complained of ocular discomfort. Eye examination at that time showed conjunctivitis, but no other abnormalities were found.

After this episode of vitamin D intoxication there were no recurrences of hypercalcaemia attributable to that therapy. However, from 1968 the patient began to show signs of progressive renal impairment with rising values of BUN and creatinine. Between

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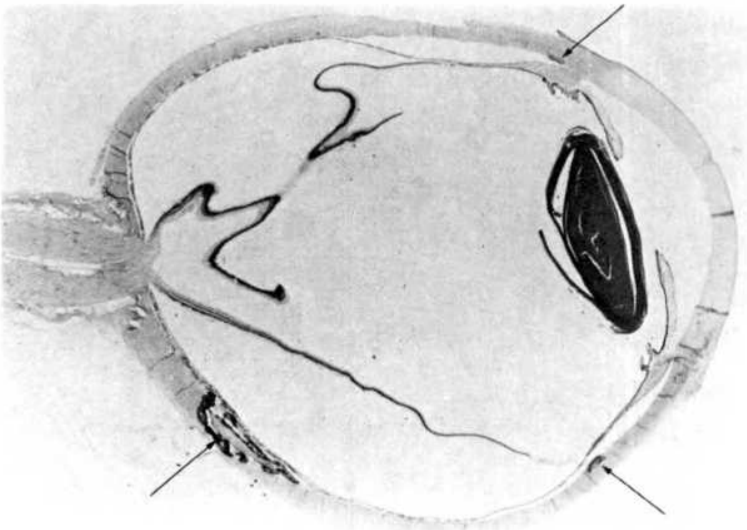

Fig. 1 *Low-power section of the globe showing areas of scleral and choroidal calcification (arrows). (H and E, × 6·4)*

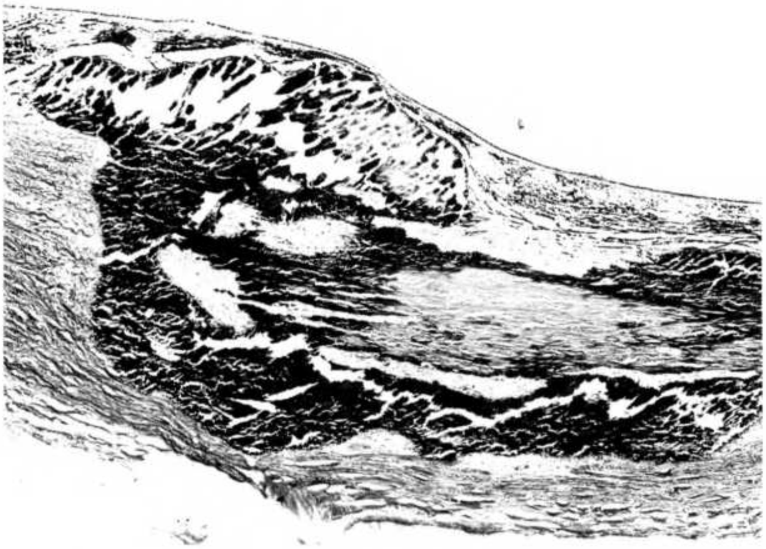

Fig. 2 *Higher power showing details of calcification of Fig. 1 with extensive scleral and choroidal calcification with sparing of the retinal pigment epithelium. (H and E, × 64)*

1976 and 1977 she required many admissions to the hospital owing to the development of chronic renal failure with progressive uraemia. Calcium levels ranged from 7·6 to 9·1 mg/100 ml (1·9 to 2·27 mmol/l), and phosphorus from 4·1 to 7·9 mg/100 ml (1·32 to 2·55 mmol/l).

Before her death she developed secondary hypertension, hypertensive encephalopathy, anuria, ascites, and secondary pancreatitis. She died on 25 April 1977 as a result of renal failure, bronchopneumonia, and pulmonary oedema.

The findings at necropsy included (1) metastatic calcifications of subcutaneous tissues, pancreas, and basal ganglia of the brain; (2) bilateral renal atrophy with uraemic changes; (3) pulmonary oedema, pulmonary effusions, and acute bronchopneumonia; (4) cardiomegaly and fibrinous pericarditis; and (5) skeletal abnormalities.

Lesions present in both eyes included (1) bullous keratopathy; (2) cataractous lens changes; (3) serous retinal detachment; and (4) bilateral scleral and choroidal calcifications (Fig. 1), confirmed by von Kossa and alizarin red stains. The calcium deposits involved almost the entire thickness of the sclera in multiple areas and replaced and compressed the overlying choroid. There was no calcification at the level of the retinal pigment epithelium or neural retina (Fig. 2).

Discussion

Pseudohypoparathyroidism is a hereditary disorder initially described by Albright in 1942. It shares with hypoparathyroidism the metabolic abnormalities of hypocalcaemia, hyperphosphataemia, and decreased urinary phosphate excretion, with attendant signs of tetany or convulsions. However, it differs from hypoparathyroidism by the absence of response to normally produced parathyroid hormone, presumably owing to a renal end-organ defect. Patients with this condition have a characteristic habitus with round face, short stature, stocky build, and short metacarpals and metatarsals. Mental retardation, hypocalcaemic cataracts, and blurred disc margins may also be present. Ectopic soft tissue calcification is a prominent part of the syndrome. These ectopic calcifications have been reported in the basal ganglia, the lens, and the subcutaneous tissues, but description of scleral and choroidal calcifications in patients with pseudohypoparathyroidism could not be found on careful review of the literature.

Multiple disease entities are associated with ocular calcification. This can occur after inflammatory, infectious, and traumatic injuries to the eye in which there are significant secondary tissue atrophy, degeneration, and necrosis as occurs in phthisis bulbi. From the detailed history available and the histopathological findings there is no evidence of previous injury to this patient's eyes which can account for the scleral calcifications found at the time of necropsy. Ocular calcification has been reported in hyperparathyroidism (Cogan *et al.*, 1948; Walsh and Murray, 1953; Jensen, 1975), in acute and chronic renal failure (Berlyne and Shaw, 1967), in sarcoidosis (Cogan *et al.*, 1948; Walsh and Murray, 1953; Crick *et al.*, 1961), in vitamin D intoxication (Howard and Meyer, 1948; Walsh and Murray, 1953; Gifford and Maguire, 1954; Leira, 1954), and in hypercalcaemia with band keratopathy (Leira, 1954). All these entities involve an imbalance of the serum calcium and phosphate levels. The presentation and the location of the calcium deposits in these diseases usually differ from the findings in our patient. In hyperparathyroidism Berkow *et al.* (1968) reported the sites of these calcifications to be the nuclei of the basal layer of the corneal epithelium, stromal keratocytes, and the nuclei of the endothelial cells of the cornea. In the hypercalcaemic state the calcium deposits found in band keratopathy are characteristically located in the Bowman's membrane in the form of spherules (Berkow *et al.*, 1968). The medical findings in our patient rule out hyperparathyroidism and sarcoidosis as causes of her scleral calcifications. Limbal scleral calcifications of a mild degree and senile scleral plaques in the area of insertion of the extraocular muscles are occasionally observed on pathological examination of eyes at necropsy. Our patient's young age and the severity of calcification observed are not consistent with ageing changes as an explanation for her calcifications.

In vitamin D intoxication metastatic calcifications of the cornea and conjunctiva have been reported (Walsh and Murray, 1953). These calcium deposits are reversible after the serum calcium level is corrected to normal levels (Wash and Murray, 1953). Our patient developed vitamin D intoxication with transient hypercalcaemia 9 years before her death. However, her calcium levels subsequently were within normal limits or lower than normal, and no recurrence of the hypercalcaemia was noted in subsequent years. We consider it highly unlikely that the severe scleral calcifications seen histopathologically could be attributed to the vitamin D intoxication which occurred 9 years earlier.

With the biochemical abnormalities of the hypocalcaemia and hyperphosphataemia in pseudohypoparathyroidism are characteristically found ectopic calcifications in the basal ganglia, the subcutaneous tissues, and the lens (Potts, 1972). By the same process it is likely that ectopic calcifications could develop in the sclera and choroid of patients with pseudohypoparathyroidism. We postulate that the biochemical imbalance of calcium and phosphate resulting from the defective response of the end-organs for the parathormone contributed principally to the formation of these ectopic calcifications in the basal ganglia and subcutaneous tissue as well as the sclera and choroid.

Our patient also had chronic renal failure with the development of progressive uraemia in the last 8 years of her life. In chronic renal failure eye calcifications have been reported in the conjunctiva, cornea, and the sclera (Potts, 1972; Porter and Crombie, 1973; Demco *et al.*, 1974; Harris *et al.*, 1971). Given this patient's renal condition at the time of her death, it is certainly possible that her compromised renal status may also have been a factor in the scleral calcium deposition. In our experience and from published reports the degree of calcification found in our patient's sclera and choroid would appear to be unusual for terminal renal failure alone. To determine the relative contribution of the renal failure and the pseudohypoparathyroid state to the ocular calcification we would suggest that radiological studies including a computerised axial tomography scan or B-mode ultrasonography, or perhaps scleral biopsies should be considered early in the course of other patients with this disease. Since renal failure is not a constant complication of pseudohypoparathyroidism, this should be possible in some patients.

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Convolution in human rods: an ageing process

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SUMMARY In a morphological survey of 73 human retinae spanning 9 decades, and including 20 retinae which were obtained from eyes enucleated for malignant melanomas, nodular excrescences were noted in the outer segments of rods with an incidence which increased with age. These structures were sectioned in both their vertical and horizontal axes and on electron microscopical examination were seen to result from the localised convolution of affected outer segments. The topographic morphology of such convolutions is described and their modes of formation are discussed.

The process of ageing and its manifestations in the cells of the human retina has for some time been a major research interest in our laboratory. These studies include the electron microscopical examination of 73 human retinae obtained from both enucleations and cadaver eyes. This series contains specimens from each of 9 decades, the youngest eye being 19 years and the oldest 90 years. The detailed morphology of the photoreceptor cells, the pigment epithelium, and Brüch's membrane have been investigated in order to establish control reference material for a future study of senile macular degenerations and inherited retinal dystrophies. We were interested therefore by a recent report purporting to show the fusion of the outer segments of juxtapositioned rod photoreceptor cells in the retina of a 47-year-old woman whose eye was enucleated because of the presence of a choroidal melanoma (Borwein *et al.*, 1977). In the present paper morphological evidence shows that this suggested fusion of appositioned cells is an age-related process occurring within the outer segments of individual rods.

Methods

One of the commonest conditions that leads to enucleation of human eyes is malignant melanoma of the uveal tract. The retinae of 20 such eyes have been studied in the present survey, with an age range spanning 7 decades. The immediate postoperative procedures varied with the individual demands of participating centres. In most centres corneal discs were trephined for subsequent use in graft procedures. One centre required the dissection of the globe and the hemisection of the unfixed tumour so that samples could be processed for tissue culture as well as histopathology. In some cases intact globes were presented immediately after enucleation, and here transcorneal incisions were made in the sagittal plain before immersion in fixative.

All eyes were fixed within minutes of enucleation by immersion in 100 ml of 0·3 M glutaraldehyde buffered in 0·1 M sodium cacodylate containing 10 mg/ml of calcium chloride with a final pH 7·4. Intact globes were progressively dissected in this solution, the cornea being removed at the sulcus sclerae after 5 minutes, the iris after a further 5 minutes, and the lens, ciliary body, and vitreous 20 minutes after the initial immersion.

After a total of 1 hour in fixative all posterior eye cups were washed in 0·1 M sodium cacodylate containing 7·5% sucrose, and in this solution experimental samples were isolated under a dissecting microscope. In all cases the tumour was isolated first and subsequently processed for conventional histopathology. Where the topography of the tumour allowed, 5 sets of samples were isolated for electron microscopical study. These were the macula and 4 bands of tissue radiating from the macula to the ora serrata in the cardinal axes. All samples were dissected so that their

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Address for reprints: Dr John Marshall, Department of Visual Science, Institute of Ophthalmology, Judd Street, London WC1H 9QS orientation with respect to the macula could be determined during subsequent ultramicrotomy, and their distance from this locus was recorded. The isolated specimens were postfixed for 1 hour in 2% osmium tetroxide in 0·2 M sodium cacodylate before being dehydrated by progressively increasing concentrations of ethanol in water and embedded in Epon 812 via epoxypropane.

Cadaver eyes were processed as above, being progressively dissected in glutaraldehyde. Where possible, the time interval between death and enucleation was recorded, as was the time between enucleation and fixation.

All sample blocks were first mounted in a Cambridge Huxley ultramicrotome and 0·8-µm sections were cut with glass knives. Most blocks were cut in at least two planes, first along the axis of the photoreceptor outer segments, and secondly at right-angles to this axis. Thick sections were stained with either toluidine blue (Meek, 1963) or basic fuchsin and methylene blue (Huber *et al.*, 1968). By means of a chuck adaptor orientated blocks were transferred to a Reichert OMU3 ultramicrotome where 400-Å (40-nm) sections were cut with a diamond knife. These sections for electron microscopy were mounted on 200-mesh copper grids and stained with uranyl acetate and lead citrate before being examined in an AEI 801 electron microscope.

Further samples, representative of each decade, were isolated after glutaraldehyde fixation, and these were frozen in isopentane precooled in liquid nitrogen before being mounted in a Slee cryostat. Frozen sections 10 µm thick were examined under a Zeiss microscope fitted with an epifluorescence attachment to determine the relative autofluorescence due to lipofuscin in the retinal pigment epithelium.

Results

Extensive observations in the present study have shown that in eyes enucleated for choroidal melanoma the morphologies of areas of retinae remote from the tumour are indistingushable from comparable areas of retinae in eyes of similar age obtained from cadavers with no known ophthalmic disease. These observations are in agreement with previous studies (Borwein *et al.*, 1977). In most cases the fixation of retinae in surgically enucleated eyes was superior to that achieved in post-mortem specimens. However, significant observations were made on both groups and statistical data were pooled.

When transverse sections of retinae in the second and third decades were examined under the light microscope, the outer segments of rod photoreceptor cells were seen as homogeneously staining elongated rectangular systems with regular parallel borders in their long axis. In samples from the central or perimacular regions such outer segments were approximately 1·4 µm in diameter and between 24 and 27 µm in length (Fig. 1). The discrete nature of these systems was apparent in sections cut along the axis of the outer segment and in those at right-angles to this axis, as in both cases a poorly stained interreceptor matrix was distinguished. In all sections the rod outer segments experienced an angular deviation between their ciliary region and the pigment epithelium, and the degree of inclination varied with retinal position, a finding common in other vertebrates (Laties and Enoch, 1977).

Changes in the morphology of rod outer segments began to appear in the fourth decade and occurred initially in the perimacular regions. In light microscopic sections such changes were seen as nodular swellings, distorting either the central region, or pigment epithelial third, of the rod outer segment profile (Fig. 1). The rod diameters were increased to between 2·5 and 3·5 µm in the region of these distortions. With increasing age such distortions became apparent in all areas of retina and in an increasing number of rod cells. By the seventh decade between 10 and 20% of the total rod population was involved.

In the electron microscope, sections of rod outer segments of young eyes showed few deviations from the typical ordered membrane array presented by the stacks of lobed discs. When such deviations occurred, they usually presented as groups of 10 to 30 discs which had become disorientated with respect to both their fellows and the boundary membrane of the cell. In some instances several such dislocations of the disc array occurred within the outer segment of a single receptor cell. A further anomaly was the occasional presence of regions of small vesicles which occurred parallel to and within the plane of the disc membranes. One or both of these phenomena occurred in some receptor cells in every sample examined. However, they never involved the boundary membrane of the cell, whose parallel configuration was always preserved in these regions. Small dislocations of the disc stacks which involved the boundary membranes were occasionally observed in young eyes, but these were always at the tips of rods, where they were surrounded by the receptor sheaths of the pigment epithelium. These occurrences usually resulted from the presence of disorganised or shed discs prior to their being phagocytosed.

In the rods of the older eyes the nodular expansions were identified as areas in which the outer segments had corrugated within their long axes

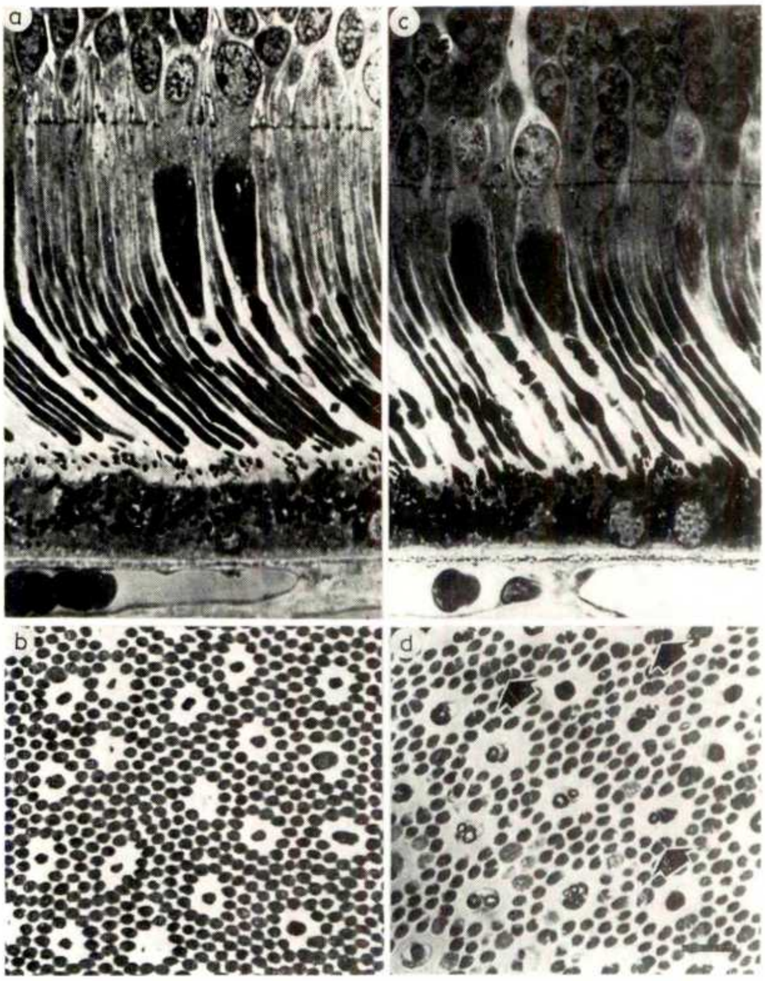

Fig. 1 (a) *Photomicrograph of a transverse section showing the receptor epithelial junction in the perimacular region of the retina of a 19-year-old male. The boundary membranes of the rods are parallel with no excrescences. Brüch's membrane is thin and the pigment epithelium contains little lipofuscin.*

(b) *Photomicrograph of a tangential section through the receptor outer segments in the retina seen in* (a) *and demonstrating the isolation of appositioned elements.*

(c) *Photomicrograph of a transverse section through the receptor epithelial junction in the perimacular region of the retina of a 54-year-old female. Nodular excrescences can be seen associated with several rod outer segments. Brüch's membrane is thicker than in* (a) *and an increased lipofuscin content is apparent.*

(d) *Photomicrograph of a tangential section through the nodular region of the outer segments shown in* (c). *Several examples of very closely appositioned elements are demonstrated* (arrowed). *The bar marker is 10 μm*

(Fig. 2). These corrugations occurred in two forms. In some rods the disc stack was displaced in a sinusoidal curve, which was compressed within the cells' boundary membrane. In other rods the whole outer segment including the boundary membrane was distorted into a series of curves. Both configurations resulted in localised corrugations in which the membranes in the ascending and descending limbs were closely appositioned. These convolutions increased the absolute length of the outer segments by 6 to 10 μm and their disc content by 20 to 40%. However, the axial distance between their cilium and the pigment epithelium remained in the same range as those of young eyes. These systems were never found to extend any distance into the receptor sheath systems of the apical membrane of the pigment epithelium. Within the sheaths small dislocations of the disc stacks were occasionally observed, and these were similar to those seen in young eyes.

When the convolutions were sectioned at right-angles to the long axis of the outer segments they appeared as a fused association of independent elements from several juxtapositioned cells (Fig. 2). The number of elements involved depended upon the number of convolutions experienced by a particular outer segment but ranged between 2 and 5 discs. The 2 modes of outer segment corrugation were clearly distinguishable, with groups of discs either being bounded by a single membrane system, or multiple boundary membranes with varying degrees of confluence. These sections also demonstrated that multiple convolutions were not confined to a single plane (Fig. 2). Similar changes have also been observed in the rod outer segments of a mature (10 to 15 years) rhesus monkey.

In human retinae in the present study inter-

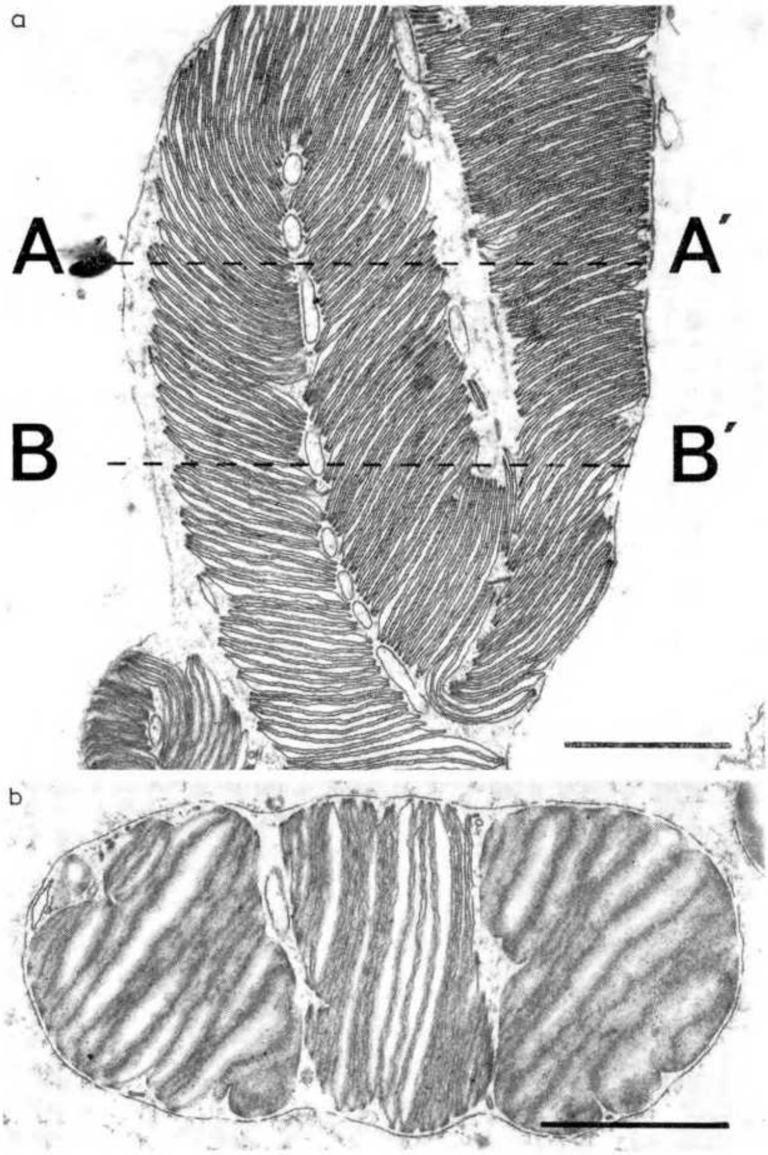

Fig. 2 (a) *Electron micrograph of a transverse section through a rod outer segment nodule showing a convolution of the disc stack and varying degrees of membrane fusion between the ascending and descending limbs. Therefore a tangential section on plane* A—A′ *would appear as a system of discs enclosed by a single boundary membrane as in* (b), *while a section on plane* B—B′ *would appear as 3 discs each with their own boundary membranes. The bar marker is 1 μm*

(b) *An electron micrograph of a tangential section through a rod outer segment nodule as described in* (a). *The bar marker is 1 μm*

receptor membrane associations were found between processes from the inner segments (Fig. 3). These were similar to those previously described in other animals (Fain *et al.*, 1976). However, in all such associations the integrity of participating membranes was maintained, and no fusion of cells was observed.

A detailed account of the changes observed in the pigment epithelium and Brüch's membrane in the present survey forms the basis of a future report. However, certain of these changes may be pertinent to those seen in the rods and are therefore briefly mentioned. In all retinae examined electron-dense deposits of lipofuscin were observed within the pigment epithelial cells, and both electron and fluorescence microscopy confirmed previous findings that such deposits increase with age (Hogan *et al.*, 1971). In young eyes lipofuscin inclusions were most abundant in epithelial cells in the macular and perimacular regions.

Discussion

Loss of order in the outer segments of photoreceptor cells occurs in response to both pathological

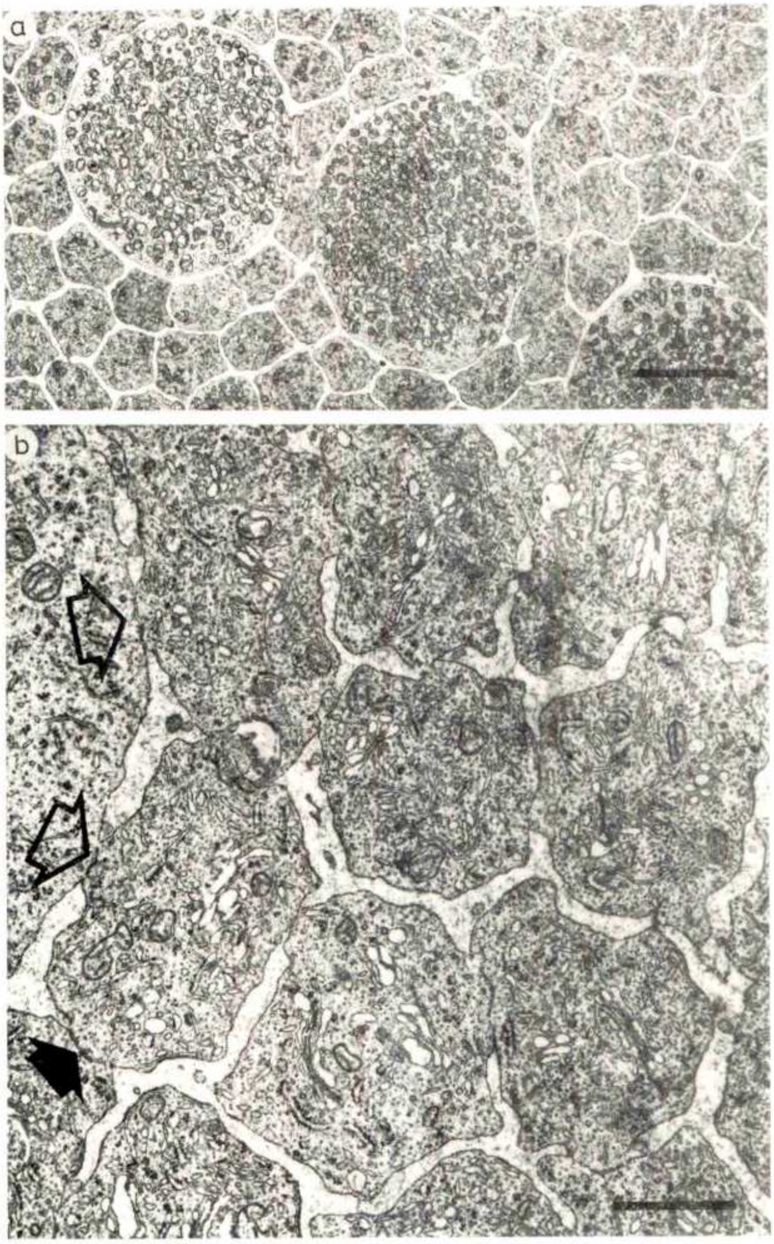

Fig. 3 (a) *Low-power electron micrograph of a tangential section through the inner segments of the photoreceptor cells in a 54-year-old woman. The interreceptor matrix is much reduced in this region of the retina but still apparent. The bar marker is 2 μm.* (b) *Electron micrograph of a similar section to that in* (a) *taken just external to the outer limiting membrane. Specialised junctional complexes may be seen both between appositioned rods* (closed arrows) *and between rods and cones* (open arrows). *The bar marker is 1 μm*

and histological processes. *In vivo* the receptors respond to a variety of disturbances in their microenvironment by failing to maintain the regular periodicity of their component disc membranes. After mild or transient injuries angular translocations of groups of discs occur within the disc stack. In episodes of severe or protracted interference with receptor homoeostasis the disc membranes degenerate into vesicular or whorl-like configurations. Typical examples of these degenerative changes are seen in such conditions as retinal detachment (Kroll and Machemer, 1968), vitamin deficiencies (Hayes, 1974), and thermal (Marshall, 1970a) or photic injury (Kuwabara, 1970). In each of these conditions the persistent changes in outer segment morphology occur as a result of fusion of membranes of both individual and juxtapositioned discs. This capacity for disc fusion is also seen in an extracellular environment and between discs originating from different receptor cells, as in the RCS rat discs shed from the rod tips, which are not phagocytosed by the pigment epithelium but come together to form huge sheets of lamellar material (Dowling and Sidman, 1962). Similar examples of disc membrane fusion are seen *in vitro* in experiments in which isolated rod outer segments are exposed to osmotic shock (Falk and Fatt, 1973) and in some histological techniques in which certain types of fixative induce such membrane fusion (Tormey, 1964). These observations imply that active processes are required for the continued maintenance of disc integrity. In contrast to disc membranes the boundary membranes of the outer segments of receptor cells remain discrete throughout each of these pathological processes and never fuse with those of neighbouring cells. The one exception to this is that portion of the boundary membrane shed from the tips of rods in the RCS rat.

In the present study areas of disorganisation arising from degenerative processes involving the discs were few in young eyes and consisted of the angular translocation of groups of discs within the boundary membranes of the rod outer segments. The vesicles seen within the plane of the discs resulted from section planes running either through the disc lobes or crenulations or through the fimbriae associated with the ciliary incisure (Pedler and Tilly, 1967). These latter incursions in the disc membrane do not maintain their stacking register on passing away from the cilium and usually revolve varying degrees in their axis of symmetry on their passage down the outer segment. Thus isolated or single multiple rows of vesicles with axial dimensions identical to those of the discs are observed throughout the length of the outer segments.

Changes in the appearance of receptor outer segments induced by histological processing are well known, and in all ophthalmic pathology laboratories the maintenance of the correct stereo spatial relationships between the neural retina and the pigment epithelium is a perennial problem. Many histological techniques result either in the detachment of the retina or in its compression against this underlying layer. In this latter group the receptor outer segments are either distorted to run at an acute angle towards the pigment epithelium, or they assume a sigmoid appearance. In affected samples all the receptors in any given area are similarly distorted. The convolutions that occur in the outer segments of older eyes in the present study (Fig. 2) are not an artefact resulting from the tissue processing techniques. They show a discontinuous distribution in histological sections of retina and an increasing incidence with age.

In many animals (Young, 1976) including monkey (Young, 1971), autoradiographic studies have shown that the discs in rod outer segments are in a state of flux. These experiments show that throughout life new discs are continuously formed in the region of the cilium, and are progressively displaced down the outer segment towards the pigment epithelium by successive disc production.

In monkeys the outer segment transit time for a disc is 9 to 13 days (Young, 1971). Old discs at the tips of the outer segments are removed by the phagocytic action of the pigment epithelium, a process which exists in dynamic equilibrium with that of disc production. Once inside the pigment epithelium the groups of engulfed discs, called phagosomes, undergo lysis, which induces their progressive degeneration (Marshall, 1970b; Ishikawa and Yamada, 1970). The degenerative end products of lysis are voided from the epithelial cells via Brüch's membrane into the choriocapillaris. From simple calculations it can be shown that in the monkey each epithelial cell destroys well over 1000 discs each day. This amounts to an enormous quantity of membranous material passing through the pigment epithelium during the life span of an animal.

This system has not been studied autoradiographically on human material, but substantive morphological evidence indicates its existence (Spitznas and Hogan, 1970). Morphological studies also suggest that the pigment epithelium in man is involved in the phagocytosis of cone outer segments (Steinberg *et al.*, 1977). The observations of increasing deposits of lipofuscin within the pigment epithelium coupled with a progressive build-up of inclusions in Brüch's membrane in ageing human eyes have been interpreted as the products of incomplete breakdown or transport of such phagocytosed outer segment material (Hogan, 1972).

It has also been suggested that both of these inclusions are manifestations of a reduction in the ability of the pigment epithelium to contend with its phagocytic load and that their presence further disturbs the dynamic equilibrium of rod growth and phagocytosis. Such perturbations could arise from a progressively increasing impedance to the outflow of phagosomal debris induced by the successive deposition of such material within Brüch's membrane. This mechanism could therefore result either in a massive build-up of debris, with the production of drusen and possibly more serious senile lesions (Sarks, 1976) or in a decrease in the rate of phagocytosis.

If the rate of disc production remains relatively constant throughout life but the rate of phagocytosis decreases, then rods must increase in length. Such an imbalance could well result in the convolutions described in the present study. This suggestion is supported by two further findings. First, the initial occurrence and subsequent highest incidence of these convolutions is in the perimacula, an area in which retinal pigment epithelial cells have a large lipofuscin content, and secondly this is an area in which drusen are commonly observed (Gass, 1973).

The degree of membrane fusion between the various limbs of the convolutions could result in three different appearances in sequential cross-sections of a single convolution (Fig. 2). Thus, where the boundary membranes of the limbs had not fused, 'isolated' elements were observed; where these membranes were confluent, the system appeared as 2 or more discs within a single membrane. And, finally, various intermediate fusions imparted an appearance similar to cytoplasmic bridges. This latter form resulted in the misinterpretation of these systems as the fused elements of appositioned receptor cells (Borwein *et al.*, 1977). The present findings are a reinterpretation arising from examination of data in both laboratories.

The functional implications of convoluted rods and the effects of their increasing numbers with age are unclear. The increase in disc content and absolute outer segment length does not seem significant because their axial length remains relatively constant through life. The increase in size of the catchment area presented to incident light in affected receptors may be of greater consequence to rod function. However, the variations between individual receptors would render analysis extremely difficult.

It is our pleasure to thank the medical and nursing staffs of the following hospitals whose co-operation in gathering samples has been essential: Addenbrookes Hospital, Cambridge; Hillingdon Hospital, London; King's College Hospital, London; Manchester Royal Eye Hospital; Middlesex Hospital, London; Moorfields Eye Hospital, London; and Victoria Hospital, London, Ontario. We are grateful to Miss E. Clarke and Mrs A. Karkahanis for technical assistance, and to both the Garrick Charitable Settlement and the Wellcome Trust for donations of scientific apparatus. We also acknowledge the US Army Medical Research and Development Command, and the Advisory Group for Aerospace Research and Development (AGARD) of NATO, for financial support.

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Vasculature of the optic nerve in anencephaly

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SUMMARY The optic nerves and globes obtained from 6 anencephalics were studied histologically and compared to normal specimens obtained from 4 stillborn infants as well as 1 case of septo-optic dysplasia. Special emphasis was placed on examination of the optic nerve, and it was found that an average of 48 vessels per high-power field were seen posterior to the lamina cribrosa in anencephalics. In contrast, control globes had an average of 12 vessels per high-power field. This suggested that an increase in the vasculature of the hypoplastic optic nerve is a characteristic feature of anencephalics.

Anencephaly is a striking congenital malformation incompatible with life. We wish to report on the unusual and previously undescribed appearance of the vasculature of the optic nerve in anencephaly. We have been impressed by the multiplicity of vessels in the optic nerve proximal to the lamina cribrosa. This observation prompted us to review the optic nerves of all the anencephalics that have come to necropsy at the Vancouver General Hospital since 1968.

Materials and methods

Material was obtained from 6 necropsies of anencephalics (9 eyes) done at the Vancouver General Hospital from 1968 to 1977.

Seven eyes from 4 stillborn babies were randomly collected from the Ophthalmic Pathology Registry of the University of British Columbia to serve as controls. One case of septo-optic dysplasia was also included for comparison.

Sections from all the eyes were stained with haematoxylin-eosin and Masson Trichrom. Vessel counts per high-power field were performed at 1 mm proximal to the lamina cribrosa.

Results

All the anencephalic eyes showed marked atrophy and/or hypoplasia of the ganglion cells, the nerve fibre layer, and the optic nerve (Fig 1). One globe showed proliferative vasculopathy similar to retinopathy of prematurity; another eye had a coloboma adjacent to the optic nerve head. A most interesting finding was an increase in the number of vessels proximal to the lamina cribrosa (Fig. 2) in all the anencephalic optic nerves. Vessel counts 1 mm proximal to the lamina cribrosa gave 48 vessels on average per high-power field, with a range of 32 to 60 (Fig. 3). In contrast the control globes had an average of 12 vessels (from 6 to 20) per high power of field (Fig. 4).

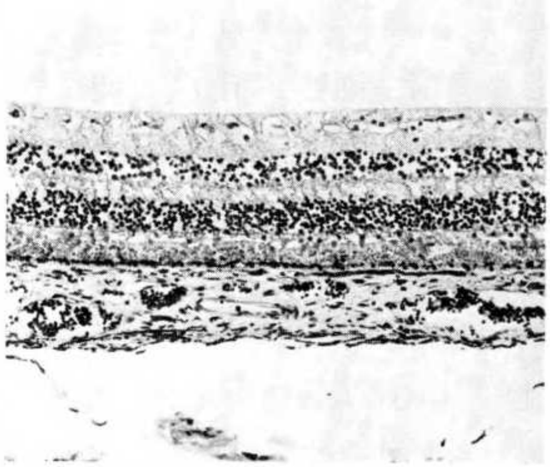

Fig. 1 *Photomicrograph of the macular area of an anencephalic showing the lack of ganglion cells. Masson,* × *75*

The case of the septo-optic dysplasia had retinal changes that were indistinguishable from anencephaly, but the appearance of the vasculature of the

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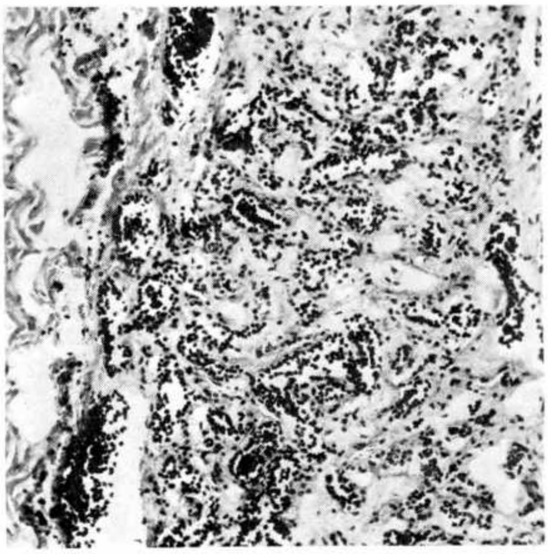

Fig. 2 *Photomicrograph of the optic nerve of an anencephalic 1 mm proximal to the lamina cribrosa. Masson, × 75*

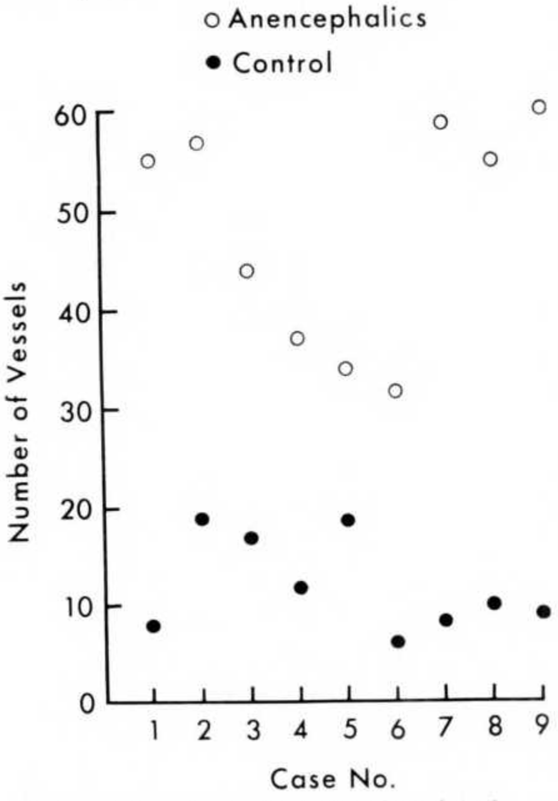

Fig. 3 *Table comparing the number of vessels in the optic nerve 1 mm proximal to the lamina cribrosa in anencephalics and controls*

optic nerve did not deviate significantly from the controls (Fig. 5). The vessel count 1 mm proximal to the lamina cribrosa was 18, which is well within the limits of the controls.

Discussion

The aetiology of anencephaly remains a mystery, but various theories have been advanced to explain

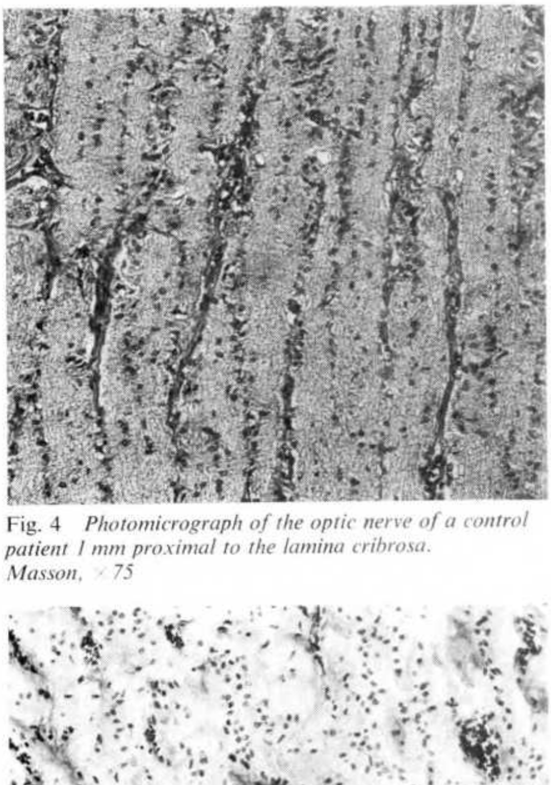

Fig. 4 *Photomicrograph of the optic nerve of a control patient 1 mm proximal to the lamina cribrosa. Masson, × 75*

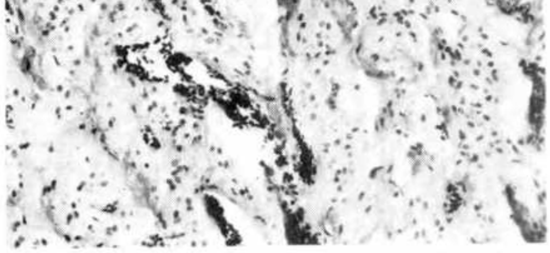

Fig. 5 *Photomicrograph of the optic nerve of a patient with septo-optic dysplasia 1 mm proximal to the lamina cribrosa. Note the lack of nerve fibres and compare its vascularity with Fig. 2. Masson, × 125*

its pathogenesis, such as failure of formation of the forebrain anlage, failure of closure of anterior neuropore, opening of the neural tube after its closure (Friede, 1975), and ischaemia (Vogel and McClenshian, 1952).

Anencephaly can be induced experimentally by various means at a critical stage of gestation (Vogel and McClenshian, 1952).

Macroscopically the eyes are of normal shape and size. Microscopically we have noted the typical and characteristic changes as described by Anderson *et al.* (1967), that is, hypoplasia and/or atrophy of the ganglion cell layer, the nerve fibre layer of the retina, and the axons of the optic nerve. Sometimes a proliferative retinopathy like that of retinopathy of prematurity occurs (Addison *et al.*, 1972). Other uncommon findings are uveal coloboma, dysplasia of the retina, corneal dermoids, and malformation of the chamber angle.

We were impressed by the striking vasculature of the optic nerve beyond the lamina cribrosa. It was seen in all sections studied, and we believe that it is pathognomonic of the condition.

In anencephaly the vault of the skull is always missing, and the skin of the temple and occiput turns over the base of the skull, encircling a mass of amorphous reddish, highly vascularised neural and mesenchymal tissue, the 'substantia cerebrovasculosa' (Vogel and McClenshian, 1952). In view of the embryological development of the optic nerve, the pathogenetic mechanism for this increased vascularity must be similar to, or part of, the mechanism that leads the development of the substantia cerebrovasculosa.

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Optic neuropathy in ketogenic diet

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SUMMARY A symmetrical, bilateral optic neuropathy is reported in 2 patients being treated with ketogenic diets for seizure control. Laboratory tests suggested a thiamine deficiency, and both patients recovered normal visual function after several weeks of treatment with thiamine. The risk of optic nerve dysfunction occurring during the treatment with a ketogenic diet can be minimised if routine vitamin B supplements are given and periodic evaluation of optic nerve function undertaken.

The ketogenic diet is now widely accepted as an effective alternative treatment for children whose seizure disorder is not controlled by standard anticonvulsant medications (Dodson *et al.*, 1976). In general, patients have not been treated by dietary therapy alone but in conjunction with standard anticonvulsant drugs. Moreover, most authorities have restricted ketogenic diet therapy to those patients in whom standard anticonvulsant therapy has not been efficacious (Dodson *et al.*, 1976; Gordon, 1977). However, since the diet has proved to be highly effective, and its reported adverse effects have been limited to infrequent abdominal pain, vomiting, and diarrhoea, a wider prescription of this form of anticonvulsant therapy has been recommended (Gordon, 1977).

Here we report the occurrence of bilateral, symmetrical optic neuropathies in 2 patients being treated with a ketogenic diet. It appears that the optic nerve dysfunction in these patients was the direct consequence of a nutritional disorder related to the diet. A thiamine deficiency appears to be the most plausible causative factor in these cases. We recommend that emphasis be placed on the need for routine vitamin supplements when instructing parents about the details of a ketogenic diet. We further suggest that a periodic assessment of optic nerve function should be an integral part of the routine medical evaluation of these children.

Patients and methods

CASE 1

This was a 5-year-old white boy. His mother's pregnancy and delivery were normal and the family history gave nothing unusual. The child was in good health in all respects until 28 months of age, when he began to have minor seizures in the form of myoclonic or akinetic attacks. Their frequency gradually increased to over 30 to 40 a day. He was treated with various drugs (barbitones, phenytoin, succinimides, and primidone) with only slight effect on the frequency and intensity of his attacks.

Examination when the boy was 38 months old showed a well-developed child, and the findings of a general physical and neurological examination (including a neuro-ophthalmic evaluation) were normal. Routine laboratory studies, skull *x*-rays, cerebrospinal fluid, and computer-assisted tomography scan were all normal. The electroencephalogram showed frequent epileptiform discharges in the form of generalised spikes, polyspikes, and spike-and-wave complexes; most of these were bilaterally synchronous.

At the age of 43 months he was begun on a 4:1 ratio high-fat diet. Over the next 2 months his seizures decreased in frequency, until at the age of 46 months he was essentially free of all seizures. He continued on a ketogenic diet in conjunction with phenytoin and primidone. At 56 months of age his parents were advised by his kindergarten teacher that he had poor vision as detected on a routine preschool examination.

On ophthalmological examination the patient read 6/24 with either eye and could not be corrected with lenses. His pupils were equal and responsive to light. He was unable to detect any of the red-green hues in the H-R-R colour test plates with either eye. The patient was not very reliable in his responses to visual field examination, but bilateral centrocecal scotomas with poorly-defined borders were noted. The ocular media were clear. The ocular fundi appeared normal even with a careful evaluation of the nerve fibre detail with red-free light. Neuro-

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logical examination revealed no abnormality other than the visual deficit.

Normal laboratory studies included a complete blood count, red blood indices, and serum electrolytes. Skull *x*-rays with optic foramina views were normal. Serum folate level was 18 ng/ml (normal 4 to 20 ng/ml); and vitamin B_{12} was 260 pg/ml (normal, greater than 200 pg/ml). Serum transketolase was 56 µg/100 ml (normal 100 to 160 µg/100 ml). Examination of the cerebrospinal fluid was entirely normal. Urinary screening for heavy metals gave a negative result.

The parents were questioned on the details of the patient's diet. They admitted that although they strictly adhered to the 4:1 ketogenic diet they did not routinely give the patient the recommended vitamin or calcium supplements. Treatment with 50 mg of thiamine daily in addition to vitamin B supplements was therefore instituted. He remained on his anticonvulsants and ketogenic diet. Six weeks after beginning treatment the patient's vision was 6/12 in either eye. He remains on a 4:1 ratio ketogenic diet and vitamin B supplements without any further visual problems.

CASE 2

This patient was a 7-year-old girl who had a history of normal development until aged 3 years, when she had abrupt onset of seizures. There was no known precipitating cause, and the family history is negative for convulsive disorders. After a few weeks of frequent grand mal seizures the patient developed akinetic seizures, myoclonic jerks, and automatisms. Routine blood studies, cerebrospinal fluid examination, skull *x*-rays, and a computer-assisted tomography scan were entirely normal. The electroencephalogram showed frequent bursts of generalised high-voltage spike-wave activity on a background of diffuse high-voltage slow waves. Over a period of 3 years various combinations of barbitones, phenytoin, primidone, ethosuximide, and acetazolamide were ineffective in treating the seizures. At the age of 6 years she was started on a 4:1 ketogenic diet, which had a dramatic effect within 6 weeks. The patient intensely disliked the diet and periodically refused to eat. However, her parents insisted on continuing the dietary therapy since it rendered the patient essentially free of seizures.

About 1 year after initiation of the ketogenic diet the patient complained of a gradual diminution in vision. On examination her best corrected visual acuity was found to be 6/36 in the right eye and 6/24 in the left eye. She read the red-green hues of the H-R-R colour test plates with extreme difficulty. The pupils were equal in size and reactivity to light. The ocular motility, media, and fundi were entirely normal. The visual field examination showed centrocecal scotomas in both eyes to a 5/1000 white test object.

Routine laboratory studies included a complete blood count, electrolytes, and urine analysis; these were all normal. Skull films with optic foramina views, a computer-assisted tomography scan, and examination of the cerebrospinal fluid were also normal. Serum transketolase was 50 µg/100 ml (normal 100 to 160 µg/100 ml). Serum folate level was 35 ng/ml (normal 4 to 20 ng/ml); and vitamin B_{12} was 240 pg/ml (normal greater than 200 pg/ml). Urinary tests for heavy metals showed nothing unusual.

In questioning the parents about the details of the patient's diet they admitted they had thought the prescribed vitamin and calcium supplements were unimportant. They had not given these to the patient for more than a year. The patient was therefore given thiamine 50 mg daily in addition to the routine vitamin B supplements. She remained on a ketogenic diet. After 6 weeks she stated she thought her vision had improved, though no change in visual acuity could be detected. After 11 weeks the visual acuity was 6/9 in both eyes. Colour vision was normal and no field defects could be demonstrated. After 3 months of treatment with thiamine and B vitamins the visual acuity was 6/5 in each eye. The patient remains on 4:1 ketogenic diet and supplemental vitamins.

Discussion

Wilder (1921) introduced the ketogenic diet for the control of childhood seizures. Despite the availability of an increasing variety of drugs the ketogenic diet remains an important alternative form of anticonvulsant therapy. The 2 major indications for it are resistance to drug therapy and/or drug toxicity. However, results of ketogenic dietary therapy have been good enough to encourage its more general use (Gordon, 1977). About 30% of properly selected children with epilepsy will have their seizures controlled while on the diet, and an additional 30% will show partial improvement in the frequency of seizure (Dekaban, 1966). Although the diet is usually restricted to the treatment of seizure disorders in childhood, some adult epileptics have benefited from it as well (Dodson *et al.*, 1976).

Ketosis is produced by giving the patient a diet consisting of a 3:1 or 4:1 fat ratio (Signore, 1973). That is, the patient is given 3 or 4 g of fat for every 1 g of nonfat. The nonfat portion is composed of variable proportions of carbohydrate and protein. An alternative diet consisting of 50 to 70% medium chain triglycerides appears to be equally efficacious and more palatable (Huttenlocher *et al.*, 1971). After 10 to 21 days the therapeutic effect of the diet becomes apparent. Some authorities (Hendley *et al.*, 1948; De Vivo *et al.*, 1973) have correlated the therapeutic effect with the degree of ketosis. However, Huttenlocher (1976) has presented evidence that the anticonvulsant action of ketogenic diets is mediated by the direct action of ketone bodies on cerebral excitability. Furthermore, it has been shown that during fasting the central nervous system can utilise ketone bodies for a large part of the substrate requirement for cerebral oxidative metabolism (Owen *et al.*, 1967). The greater effectiveness of the ketogenic diet in controlling seizures in children may be related to the fact that children seem to have a greater capacity than adults to oxidise ketone bodies (Krause *et al.*, 1974).

It is noteworthy that despite the significant metabolic alterations that occur as a consequence of a ketogenic diet serious complications have been infrequent. Mild gastrointestinal disturbances such as abdominal pain, vomiting, and diarrhoea may occur, but they rarely cause trouble. Hyperuricaemia and hyperlipidaemia may develop, and the long-term effects of these disturbances have been cited as potential hazards requiring further investigation (Gordon, 1977). A more serious complication has been the development of dehydration and severe metabolic acidosis in some mentally retarded children treated with a ketogenic diet during intercurrent febrile illnesses (Dodson *et al.*, 1976).

In this paper we report 2 patients who, while being treated with ketogenic diets, developed bilateral, symmetrical optic neuropathies. The presence of symmetrical optic neuropathies with bilateral centrocecal scotomas should prompt the consideration of a nutritional or toxic amblyopia (Harrington, 1971). We believe the most likely cause of optic nerve dysfunction in these 2 patients is thiamine deficiency.

The role of thiamine deficiency in our patients' optic neuropathies is suggested by: (1) The fact that a ketogenic is deficient in B vitamins (Dodson *et al.*, 1976); (2) the failure of both sets of parents to administer the prescribed B vitamin supplements; (3) the low serum transketolase levels, strongly suggesting significant thiamine deficiency in both patients (Dreyfus, 1965); (4) the reversal of the visual defects as a consequence of treatment with thiamine supplements despite continuation of the ketogenic diets and anticonvulsants; and (5) the fact that a pure thiamine deficiency has been shown to cause optic nerve degeneration in experimental animals (Rodger, 1953).

We specifically investigated other potential metabolic causes of optic nerve dysfunction. Serum folate and vitamin B_{12} levels were normal in both patients. There was no history of exposure to toxic substances, including those most commonly associated with this kind of optic neuropathy. Urinary tests for heavy metals were negative. We considered the possibility that the anticonvulsants were responsible. However, although it is well recognised that visual blurring may occur during acute intoxication with some anticonvulsants (Patel and Crichton, 1968), we are unaware of any data correlating optic neuropathy with standard anticonvulsants in therapeutic doses. The prompt recovery of both patients after treatment with thiamine and B vitamin supplements strongly suggests a vitamin deficiency as the cause of the optic nerve disturbance in both patients.

A recent report of a comparable type of optic neuropathy occurring in patients adhering to a low-carbohydrate high-protein diet for weight reduction also implicated thiamine deficiency as the cause of optic nerve dysfunction (Hoyt and Billson, 1977). Thiamine deficiency is involved in several disorders of the central nervous system. It is well established as the cause of the Wernicke-Korsakoff syndrome (Cogan and Victor, 1954). However, optic nerve dysfunction is uncommon in this disorder. It seems likely that thiamine deficiency is involved in the aetiology of alcohol amblyopia (Dreyfus, 1965). The production of optic nerve degeneration in rats fed a thiamine-deficient diet lends support to the thesis that pure thiamine deficiency can cause optic nerve dysfunction (Roger, 1953).

Clinically significant thiamine deficiency has become an uncommon condition in non-alcoholic patients since the introduction of enriched breads and cereals (Lane *et al.*, 1942). However, the ketogenic diets used in the treatment of childhood seizures and the low-carbohydrate/high-protein weight reduction diets are both thiamine deficient. Although thiamine requirements decrease as carbohydrate intake decreases, a thiamine deficiency may develop after long-term use of either of these diets. Therefore, optic nerve dysfunction is a potential complication of the diets if supplemental vitamins are not taken. We suggest that when prescribing the diets physicians should place special emphasis on the necessity of B vitamin supplements. In addition, periodic evaluation of optic nerve function should be incorporated into the examination of these patients.

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Assessment of unilateral afferent pupillary defects by pupillography

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SUMMARY A pupillographic technique, an adaptation of the swinging light test, is described for the measurement of unilateral afferent pupillary defects. In normal persons it yielded accurate, reproducible estimates of the magnitude of artificial afferent defects made with neutral filters of 1 to 4 log units density. In 15 studies on 8 patients with unilateral optic neuritis and 2 with unilateral compressive lesions the measured afferent pupillary defects correlated closely with both visual acuity and visual threshold deficits. Measurement of the pupillary defect underestimated severe degrees of impairment revealed by visual threshold determination. Discrepancies between pupillary defect and visual acuity were observed in the 2 patients with compressive lesions and in 1 patient who had a central scotoma 4 months after an attack of optic neuritis.

Clinical assessment of the severity of damage caused by an attack of optic neuritis may be based on the appearance of the optic disc or on the determination of visual acuity, colour vision, visual field defects, the macular light threshold, the occipital visual evoked response (VER), or the pupillary light reflex. Previous pupillographic studies have indicated that the light reflex is qualitatively normal in this condition and that its reduced amplitude can be matched by eliciting the light reflex in a normal eye with light of reduced intensity (Lowenstein, 1954a; Thompson, 1966).

In the present study of unilateral afferent defects this observation has been employed in an adaptation of the swinging flashlight test (Levatin, 1959). With this technique the requisite degree of attenuation of the stimulus light applied to the normal eye has been used as a quantitative measure of the defect in the affected eye. The reliability of the method is assessed by using artificial afferent defects in normal persons and a small study performed on patients with unilateral optic nerve lesions.

Methods

Subjects. Measurements were performed on 13 healthy volunteers aged 20 to 30 years and on 10 patients with clinically diagnosed unilateral afferent defects. Outline clinical details of the patients are given in the 'results' section.

Visual acuity. The corrected visual acuity of both eyes in patients was recorded. For quantitative comparison with other measurements the values obtained were scaled for visual efficiency by the method of Snell and Sterling (1925). Visual acuity less than 6/60 was scaled zero efficiency.

Pupillography. Pupil diameters were recorded continuously in the dark with a Whittaker Corporation Series 1800 binocular infrared TV pupillometer. Light reflexes were elicited with light from Sylvania 2-watt tungsten arc lamps. Each lamp output was focused on the model pupil and thus, as closely as possible, in the plane of the subject's pupil with a beam diameter of 2 mm, that is, smaller than the pupil diameter (Maxwellian view). The mean angle of incidence was 7° 31′ to the temporal side of the visual fixation point and in the same horizontal plane. Light intensities were varied with Kodak Wratten neutral density filters.

Visual threshold. Visual thresholds in both eyes of patients were obtained with the pupillometer light sources by a forced-choice method adapted from that described for the measurement of taste thresholds by Harris and Kalmus (1949). The patients were dark-adapted by wearing dark red goggles for 30 minutes. At each light intensity 3 sets of 3 auditory signals, 4 seconds apart, were given, 1 signal in each set being accompanied by a light stimulus of 0·5 second duration from the pupillometer as described above. Correct interpretation of

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when the light stimuli were given was taken to indicate that the subject could see the light, and the intensity was therefore above threshold. If the subject interpreted correctly, further sets of signals were given with successively lower intensities of light stimuli until the subject made errors. The visual threshold was recorded as the lowest intensity (in log density units of filtration) which could be correctly distinguished from no light at all. The chance of guessing correctly is 1/27 ($P = 0{\cdot}037$).

Pupillary afferent defect. Artificial unilateral afferent defects were created in healthy volunteers by placing neutral density filters (1 to 4 log units) before one of the stimulus lights. The magnitude of this artificial defect in volunteers and of the real defect in patients was assessed by a modification of the swinging light test. The volunteers were tested on two occasions at least 1 week apart, defects of 1 and 2 log units being tested without, and defects of 3 and 4 log units with, dark adaptation. Left and right eyes were subjected to alternating light stimuli of 1 second duration without interruption and pupil responses to about 12 pairs of stimuli recorded. Responses were obtained from 1 pupil only, preliminary measurements being used to assess that this pupil was not subject to alternating contraction anisocoria (Lowenstein, 1954b). Neutral density filters were subsequently added to the light sources illuminating the unaffected eye so as to obtain approximately balanced responses to alternating stimulation. The test was repeated using 5 or more filter values, differing by 0·2 log unit steps, around the approximate balance point. The mean difference in pupil response between the 2 sides, after exclusion of the first 4 responses, which were usually larger than the remainder, was plotted graphically against filter values and the balance point (in log units of filtration) obtained by linear regression, by the method of least squares (Snedecor and Cochran, 1967). Examples of pupil diameter traces at 3 filtration values and of 2 regression plots are given in Figs. 1 and 2 respectively.

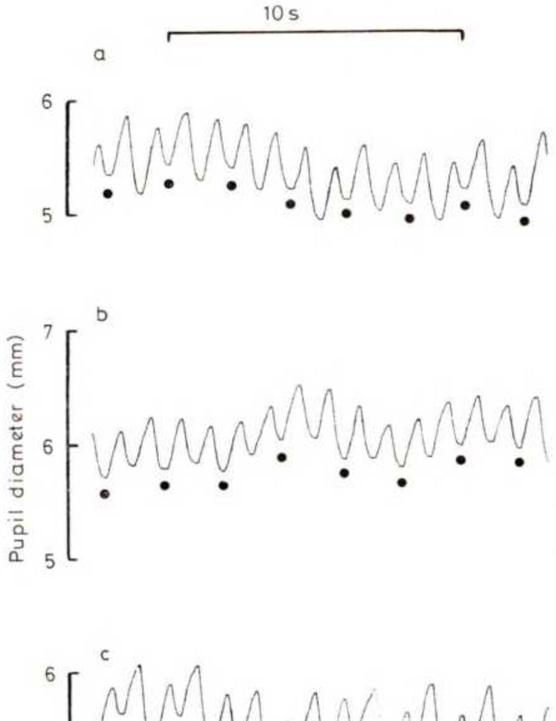

Fig. 1 *Pupil response of normal subject with right-sided 1 log unit artificial afferent defect following alternating light stimulation (● = left eye) at different stimulus intensities. Filter added* (L): (a) *1·4;* (b) *1·0;* (c) *0·4 log units. Pupil responses are approximately balanced in* (b)

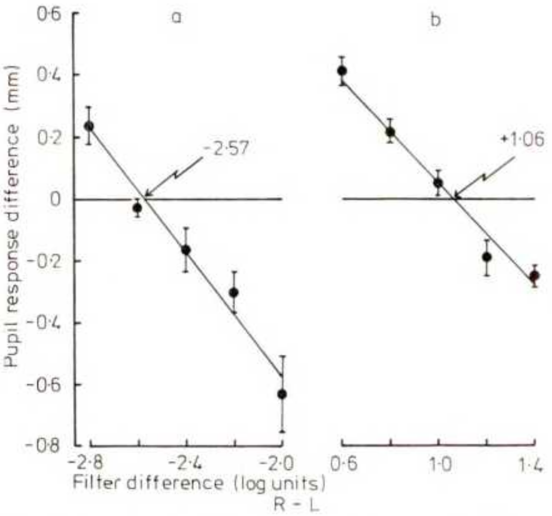

Fig. 2 *Pupil contraction differences (mean ± SEM) following alternating light stimulation at different relative stimulus intensities in:* (a) *Patient no. 1; and* (b) *normal subject no. 1 with 1 log unit artificial afferent defect*

Results

ARTIFICIAL AFFERENT DEFECTS IN VOLUNTEERS

The results of duplicate measurements of artificial afferent defects with 95% confidence limits and correlation coefficients are given in Table 1. The precision of the method was such that 16 of the 26

Table 1 *Duplicate measurements of artificial afferent defects in 13 normal persons*

No.	*Applied defect (log units)*	*Pupil afferent defect (log units)*		
		Mean	*95% confidence limits*	*−r**
1	1·0	1·06 1·14	0·75–1·38 0·81–1·48	0·93 0·92
2	1·0	1·06 1·25	0·56–1·57 0·72–1·79	0·85 0·84
3	1·0	0·90 1·16	0·62–1·17 0·87–1·45	0·95 0·94
4	1·0	0·89 1·03	−0·13–1·91 0·52–1·57	0·87 0·84
5	2·0	2·14 1·96	1·64–2·64 1·31–2·60	0·85 0·79
6	2·0	1·85 1·57	1·36–2·35 0·96–2·15	0·86 0·81
7	2·0	2·09 2·14	1·11–3·08 1·72–2·57	0·84 0·89
8	2·0	1·65 2·16	0·68–2·58 1·56–2·77	0·67 0·81
9	3·0	3·11 2·79	2·61–3·62 2·23–3·33	0·85 0·83
10	3·0	2·79 3·08	2·04–3·52 0·88–5·35	0·75 0·40
11	3·0	3·54 3·60	2·91–4·20 2·86–4·40	0·79 0·74
12	4·0	3·68 3·68	2·08–5·13 2·75–4·57	0·51 0·68
13	4·0	4·20 4·31	3·50–4·92 3·48–5·17	0·76 0·70

*Correlation coefficient for pupil contraction difference *v.* filter value

determinations fell within 0·2 log units of the correct value and only 3 determinations differed by more than 0·4 log units. The correlation coefficients indicated that the precision was slightly better at low than high afferent defect values. A paired *t* test indicated that the measured defect did not differ significantly from the correct value ($t = 0.64$, $P > 0.05$), and the measurement showed satisfactory repeatability (intrapair correlation $r = 0.98$).

AFFERENT DEFECTS IN PATIENTS

Visual acuity, visual threshold, and pupil afferent defect values obtained in 10 patients with clinically diagnosed unilateral defects are given in Table 2. Acuity and threshold differences and afferent defects are expressed as right minus left values; negative figures therefore indicate right-sided, and positive figures left-sided, defects. All but 2 patients (2 and 8) showed impaired threshold and/or an afferent defect on testing.

Repeated measurements were performed on 3 patients (nos. 1, 9, and 10) within a few weeks of the onset of retrobulbar neuritis. In 2 of these (9 and 10) clinical improvement was accompanied by improvement in the visual threshold and reduction of the measured afferent defect.

Comparison of the magnitude of the intraocular differences in visual acuity (the scaled measure being used) and threshold and the afferent defect showed substantial agreement between individual values. High correlation coefficients between the 3 para-

Table 2 *Visual acuity, threshold, and afferent pupillary defect of 10 patients with unilateral disease*

Case no.	*Sex*	*Age*	*Diagnosis*	*Weeks since onset of symptoms*	*Visual acuity*		*Scaled*			*Visual threshold (log units)*			*Afferent pupillary defect (log units)*
					R	*L*	*R*	*L*	*Diff.*	*R*	*L*	*Diff.*	
1	M	25	R optic neuritis	2 6	<6/60 6/60	6/5 6/5	0 20	103 103	−103 −83	4·9 4·5	8·4 8·6	−3·5 −4·1	−2·57 −2·48
2	M	29	R optic neuritis	104	6/5	6/6	103	100	+3	8·7	8·6	+0·1	+0·32
3	F	46	R optic neuritis	78	6/12	6/5	84	103	−19	7·9	8·4	−0·5	−0·78
4	M	20	L optic neuritis	52	6/5	<6/60	103	0	+103	9·3	5·8	+3·5	+2·87
5	F	15	R optic nerve meningioma	22	6/12	6/5	84	103	−19	4·8	8·8	−4·0	−1·36
6	M	31	L optic neuritis	26 30	6/5 6/5	6/36 6/36	103 103	41 41	+62 +62	8·8 8·1	4·6 7·3	+4·2 +0·8	+1·52 +1·14
7	M	18	R orbital compression	8	6/5	6/5	103	103	0	8·5	8·5	0	−1·08
8	F	29	L optic neuritis, central scotoma	16	6/6	6/36	100	41	+59	8·2	8·4	−0·2	0
9	F	18	R optic neuritis	3 5	6/18 6/6	6/5 6/5	70 100	103 103	−33 −3	6·4 8·2	7·5 8·3	−1·1 −0·1	−0·74 −0·03
10	F	41	R optic neuritis	1 2 3	6/60 6/18 6/6	6/5 6/5 6/5	20 70 100	103 103 103	−83 −33 −3	5·2 7·1 8·2	8·3 8·5 8·5	−3·1 −1·4 −0·3	−1·50 −1·00 −0·50

meters were found as indicated in the following matrix:

	Threshold	*Afferent defect*
Acuity	0·86	0·93
Threshold		0·91

The 2 patients with compressive lesions (nos. 5 and 7) had somewhat greater afferent defects than expected from their impairment of visual acuity. By contrast, the patient with a residual central scotoma following optic neuritis (no. 8) had no afferent defect despite severe impairment of acuity. A graphic plot of afferent defect against threshold difference (Fig. 3) shows that the former measurement relatively underestimated severe degrees of impairment. The linear regression between the measurements differed significantly from that expected from their complete agreement (t =6·68, P<0·001).

Discussion

The present study has demonstrated a pupillographic adaptation of the swinging flashlight test which can provide an objective assessment of the unilateral afferent pupillary defect. In normal persons the technique yielded close estimates of artificial defects, and in patients it provided measurements which correlated closely with both visual acuity and light perception threshold. In 2 patients with optic neuritis of recent onset repeated measurements over a period of 2 weeks showed a reduction in the afferent pupillary defect which coincided with improvement in both acuity and light threshold. The technique can therefore provide unbiased confirmation of clinical recovery. With the exception of the VER all other tests used for the assessment of afferent visual pathway are subjective and liable to error in both patient and observer.

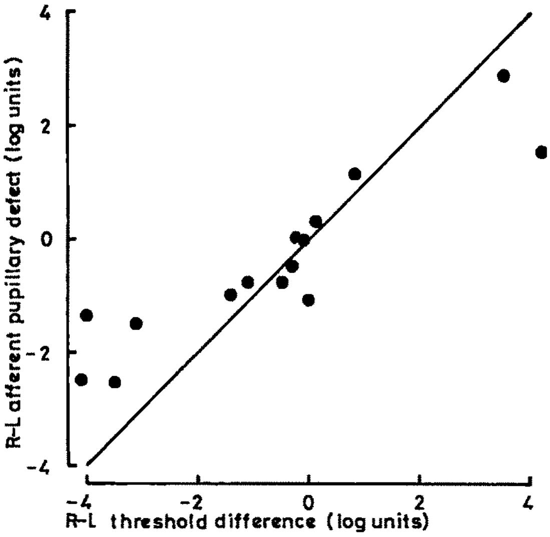

Fig. 3 *Relationship between visual threshold difference and relative pupillary afferent defect* (n = 15). *Line drawn depicts agreement between the measurements*

The measurements obtained on 3 of our patients revealed discrepancies between the magnitude of the afferent defect and impairment of visual acuity. In the conditions used it is likely that these arose because the 2 tests measured the function of different parts of the retina. While acuity involves macular vision, the pupillary response was elicited with light falling on the whole retina, representing a mass response. The exact size and position of the area stimulated is, however, uncertain. It is well known that at high intensities of illumination the visual acuity decreases as a result of dazzle (Moses, 1975). This decrease is believed to be a manifestation of neural inhibition within the retina.

It is inherent in the method that the assessment of the defect depends on the application of stimuli of different intensity to the 2 eyes. In the disease-affected eye, necessarily stimulated by the brighter light, there should be retinal adaptation (both photochemical and neural) to the greater stimulus (Newell and Ernest, 1974). If this occurred, our technique would have *over*estimated the magnitude of the defect, whereas by comparison with the visual threshold determination it was, in practice, *under*-estimated. This finding cannot be explained at present, although it is possible that the pathological process directly affects neural light adaptation.

One obvious limitation of this technique is that it provides merely a comparison between the 2 eyes and it is less useful in patients with bilateral lesions. The same drawback has been noted by others studying optic nerve disease. Thus, Rushton (1975) noted this limitation among others when he reported the use of the Pulfrich pendulum to demonstrate abnormal delay in the visual pathway in patients with multiple sclerosis. Halliday *et al.* (1972) observed delayed latency in visual evoked responses to pattern-reversal stimulation in patients with optic neuritis, and they showed that some abnormal delay persisted after full clinical recovery. Using a similar technique, they later showed (Halliday *et al.*, 1973) that clinically silent plaques of presumed demyelination could be demonstrated in the primary visual pathways of patients with multiple sclerosis, in whom optic neuritis had not occurred. These findings were substantiated by Asselman *et al.* (1975). It must therefore be emphasised that the technique used here can provide only a relative estimate of the afferent pupillary defect.

Work is in progress in our laboratory to compare pupillographic and VER findings in healthy volunteers and in patients at intervals after episodes of optic neuritis. In this way it may be possible to localise demyelinating foci more accurately by comparing the anterior part (shown by the pupil response) with the combined anterior and posterior parts (shown by the VER) of the visual pathway. One object in our current studies is to establish standards for the magnitude and velocity of the pupillary light reflexes at different levels of illumination, against which defects arising from optic nerve damage can be assessed.

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Pituitary adenoma and orbital haemangioma: a case report

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SUMMARY A 43-year-old woman with a pituitary tumour had unexplained right proptosis. Orbital *x*-rays and ultrasound were normal, but computed tomography showed an intraconal tumour, which had typical features of a cavernous haemangioma on carotid angiography. Both tumours were resected and confirmed histologically.

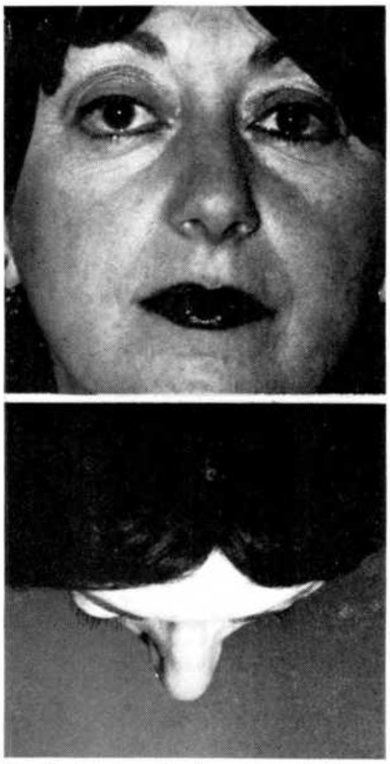
About 8% of most series of intracranial tumours are pituitary adenomata (Zülch, 1965), the majority of these being chromophobe. The most usual presentation is with bitemporal field defects and visual failure (Martins, 1974). Cavernous haemangiomata are the commonest type of orbital tumour (Reese, 1964). Their cardinal symptom is proptosis, but they may also produce papilloedema, optic atrophy, and diplopia (Duke-Elder, 1974). We report here the rare, and presumably chance, association of both these tumours in the same patient. Although clinically a difficult problem, the patient displayed classical radiological features of both these tumours. The value of computed tomography is stressed in this situation.

Case report

The patient, a 43-year-old woman, had been noted by her friends to have right proptosis 1 year before being referred to hospital. This had slowly progressed. Three months later she had developed slight intermittent diplopia, mainly on upgaze, with vertical displacement of the images. For 6 months she noticed a faint 'haziness' of vision bilaterally, more marked in her right eye.

She had had decreased libido and secondary amenorrhoea for 26 years after a normal menarche, and for many years she had tended to gain weight and suffered from cold intolerance. She had been unsuccessfully treated with 'thyroid tablets' 10 years ago. For several years she had worn a wig because of sparse capital hair.

She was initially assessed ophthalmologically and was referred to the Maida Vale Hospital after a normal orbital ultrasound study and with a skull *x*-ray showing an enlarged pituitary fossa.



Figs. 1a, b *Right proptosis viewed from in front and above*

Examination showed a moderately overweight, normotensive woman. Scalp hair was thin and dry, and pubic and axillary hair, though sparse, was of normal distribution. There was 5 mm of axial proptosis on the right (Fig. 1). Elevation of the right

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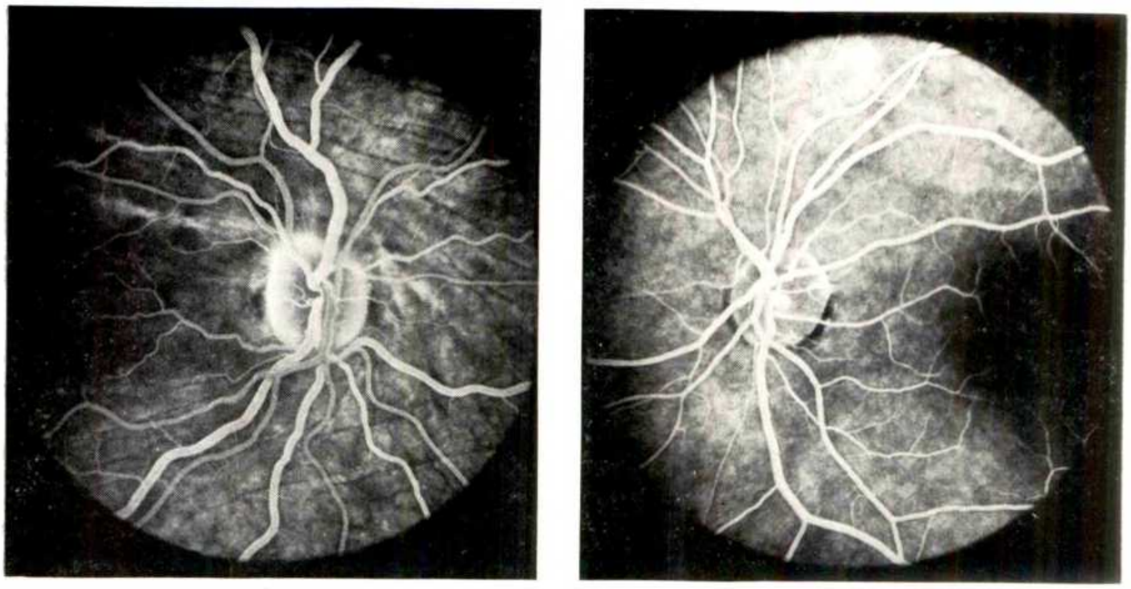

2a
2b

Figs. 2a, b *Fluorescein angiogram. Both sides are given for comparison. There is slight disc swelling on the right and choroidal folds are visible*

eye was restricted to 50%, and this was more marked on adduction. There were no orbital bruits. Visual acuity corrected to 6/7·5 right and 6/6 left. There was hereditary deuteranomaly. Initial Goldmann and tangent screen fields were full, but repeat testing after 6 weeks revealed a subtle right caecocentral defect and left upper temporal restriction. The right disc was slightly hyperaemic; there were choroidal folds superotemporally on the right.

Investigations. The erythrocyte sedimentation rate was raised at 37 mm in 1 hour. The remaining haematological and biochemical indices, including plasma and urinary osmolalities, were normal. Endocrinological studies showed a euthyroid and eucortisol state, and an insulin tolerance test was normal. There was marked elevation of serum prolactin to greater than 4900 mU/l (normal 0 to 360 mU/l). Fluorescein angiography confirmed the right disc oedema and choroidal folds (Fig. 2). Pattern visual evoked responses were bilaterally abnormal in wave form, more so on the right, and half field responses were consistent with early compression involving the decussating fibres at the chiasm.

Radiological investigations. Plain *x*-rays and tomograms of the skull showed asymmetrical ballooning of the sella turcica typical of a pituitary tumour (Fig. 3). There was no calcification or other abnormality. In particular the orbits appeared normal on polytomography. Orbital B-scan ultrasound was normal. Computed tomography (Fig. 4) showed a mass of increased attenuation, without calcification, which enhanced homogeneously, filling the ballooned sella and suprasellar cisterns. There was an evenly dense, rounded, intraconal mass with clear-cut edges displacing the right globe and obviously causing the proptosis. In common with most orbital masses it enhanced considerably after intravenous contrast medium.

Right carotid angiography showed a diffuse capillary blush supplied by hypophyseal arteries outlining the pituitary and suprasellar tumour. There was no displacement of any vessels by this tumour. The superior ophthalmic vein was deviated and curved superiorly and was somewhat narrowed but not obstructed by the intraconal mass. Lakes of contrast filled within part of the tumour in the venous phase (Fig. 5).

Pneumoencephalography confirmed the outline of the suprasellar mass and showed the anterior recesses of the third ventricle to be elevated and splayed apart by it.

Operation. A right frontal craniotomy was performed for excision of the pituitary tumour (Mr L. Symon). The tumour proved difficult to detach from the undersurface of the chiasm, but it was excised fairly completely with its capsule. The

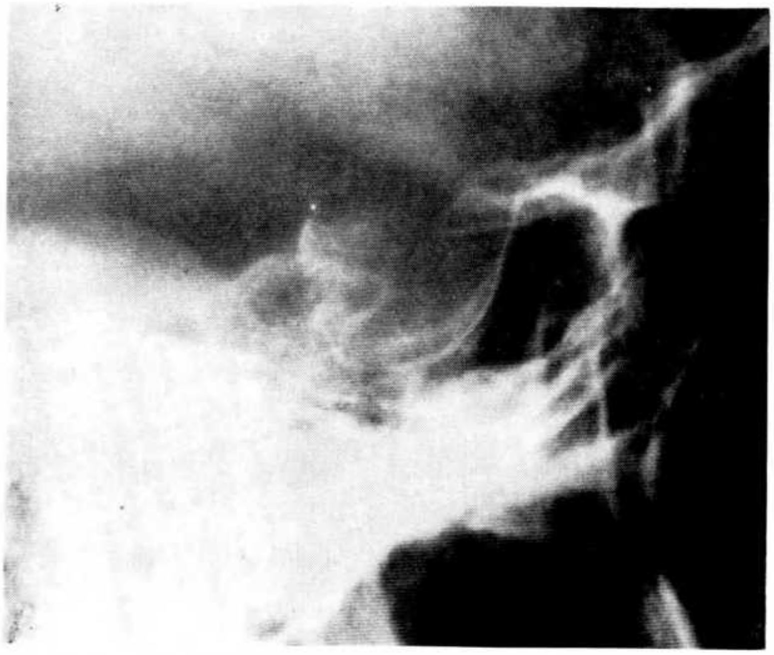
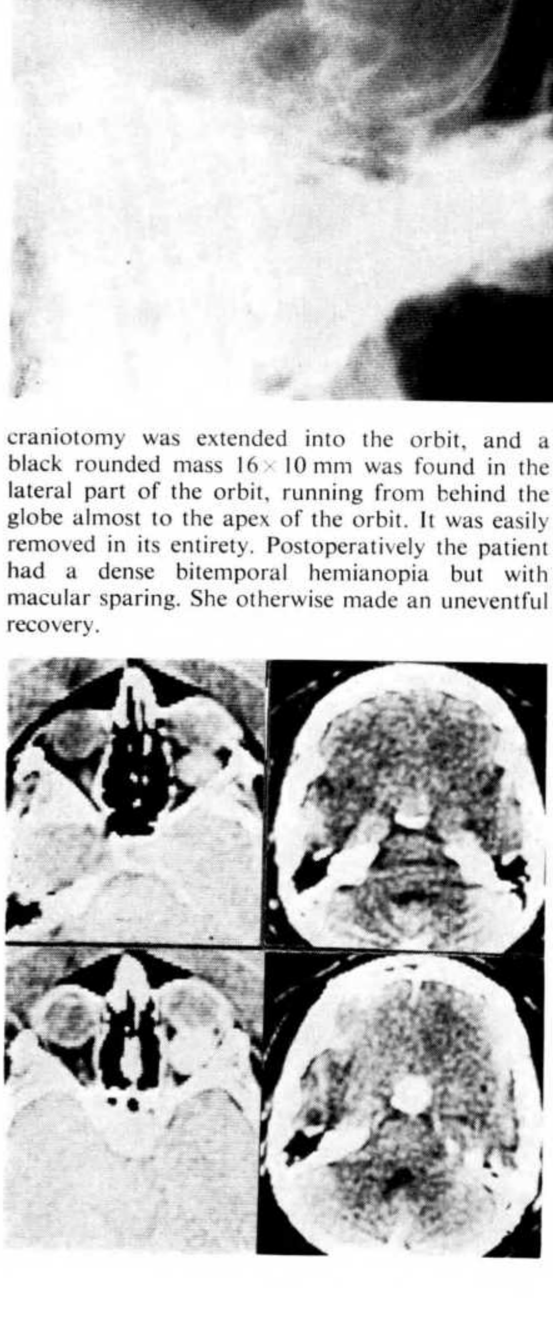


Fig. 3 *Skull* x-*ray. Lateral projection. The pituitary fossa is asymmetrically ballooned by an intrasellar mass*

craniotomy was extended into the orbit, and a black rounded mass 16 × 10 mm was found in the lateral part of the orbit, running from behind the globe almost to the apex of the orbit. It was easily removed in its entirety. Postoperatively the patient had a dense bitemporal hemianopia but with macular sparing. She otherwise made an uneventful recovery.



Histology. The tumours showed classical histological features of chromophobe adenoma and cavernous haemangioma.

Discussion

The ballooned sella turcica and the capillary blush supplied by hypophyseal arteries to a tumour extending from the sella through the suprasellar cisterns are the classical radiological features of a pituitary adenoma. The computed tomographic features are also those commonly found in pituitary adenomas, 75% of which show increased attenuation on computed tomography and most of which show homogeneous enhancement after intravenous contrast medium. Pneumoencephalography, which is performed routinely in our unit

Fig. 4 *Computed tomography before* (above) *and after intravenous contrast medium* (below). *The scans were taken at the level of the orbit and sella (window level = -6, window width = 100) and suprasella (window level + 18, width 40). There is a spherical intraconal mass with clear-cut edges in the right orbit displacing the globe anteriorly. It is of high attenuation and homogeneous but without evidence of calcification. There is another mass of greater-than-brain attenuation without calcification in the pituitary fossa extending into the suprasellar cistern. The right side of the dorsum is deviated posteriorly. Both tumours show homogeneous enhancement after contrast medium*

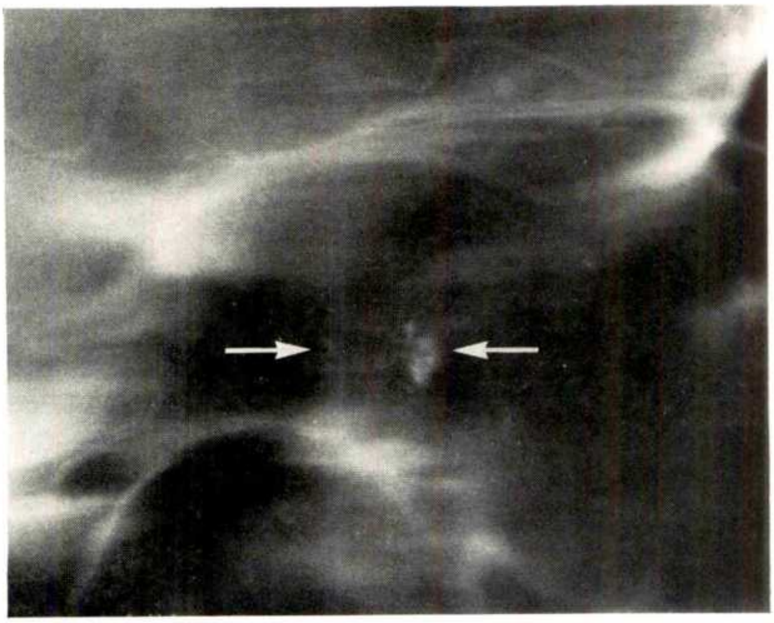


Fig. 5 *Right internal carotid angiotomogram. Venous phase. There is a cluster of dilated veins* (see arrows) *in the middle and posterior thirds of the right orbit within the mass. These appearances are typical of a cavernous haemangioma*

to show the relationship of a pituitary mass to optic chiasm and nerves prior to surgery, further confirmed that the tumour extended from the pituitary fossa into contact with the optic chiasm.

In the presence of a pituitary tumour and with a normal orbital ultrasound the possibility of an endocrine exophthalmos was considered clinically. It seemed unlikely with choroidal folds, pronounced unilateral involvement, and absence of thyrotrophic abnormalities. Computed tomography left no doubt that the proptosis was due to an intraconal orbital tumour and showed no evidence of thickening of the rectus muscles such as occurs in thyrotrophic exophthalmos. Computed tomography shows the localisation and extent of intraorbital tumours in the great majority of cases (Lloyd and Ambrose, 1977). It is usually possible to distinguish benign intraconal tumours, which typically show clearly demarcated edges from infiltrating orbital masses, which are much less well defined and may obliterate the outlines of normal structures within the orbit. A haemangioma is the commonest cause of a rounded, well-demarcated, homogeneous, high-attenuation mass, though it is precisely similar to the less-common neurofibroma and to some optic sheath meningiomas. The latter, however, may contain calcification. There is generally no difficulty in distinguishing an optic nerve glioma, which tends to be orientated in the axis of the nerve and inseparable from it. Since there is no blood-brain barrier in the orbit, all intraorbital tumours may enhance and cannot be distinguished by using this technique.

Most orbital haemangiomas show abnormal circulation. This is sometimes rapid, with arteriovenous shunting, but the appearances shown in our patient of cavernous blood spaces outlining with contrast medium in the venous phase are typical of this type of lesion. There is, in addition, a variable amount of solid tumour which causes a mass effect. The deviation of the ophthalmic veins without obstruction is helpful in distinguishing localised benign masses from infiltrating orbital lesions.

We are grateful to Professors W. I. McDonald and L. Symon, who kindly permitted us to publish this case. Mr M. D. Sanders permitted us to publish Figs. 1 and 2. Photographic assistance was provided by the Departments of Medical Illustration at the National Hospital, Queen Square, and the Middlesex Hospital.

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Normocapnic anaesthesia for intraocular surgery

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SUMMARY Measurement of intraocular pressure (IOP) by applanation tonometry in 23 patients undergoing lens extraction showed that a normocapnic general anaesthetic technique with controlled ventilation of the lungs (IPPV) reliably reduced the IOP by 50% for the duration of the operative period. This was not associated with large falls in systemic arterial pressure which are often a feature of spontaneously breathing halothane anaesthesia for eye surgery. Normocapnia and IPPV were easy to achieve by use of the single-limb coaxial Bain anaesthetic breathing circuit in conjunction with an electrically driven, small, and inexpensive ventilator while the anaesthetic mixture of 33% oxygen and 0·5% halothane in nitrous oxide was delivered at a rate of 70 ml/kg body weight per minute.

It is only in recent years that general anaesthesia has been used for the majority of patients undergoing eye surgery. Local anaesthesia continues in use, especially since most patients presenting for intraocular surgery are elderly and often suffer from cardiovascular, respiratory, or metabolic diseases. In addition coughing, straining, or vomiting resulting from the administration of a general anaesthetic can produce large rises in intraocular pressure (IOP). However, the supremacy of local anaesthesia has now been abolished by improvements in general anaesthesia resulting from a wider choice of drugs and techniques, so that the surgeon enjoys a relaxed atmosphere and the apprehension of the patient is eliminated.

Most general anaesthetic methods produce a fall in IOP (Magora and Collins, 1961), but this ideal condition is most easily produced by a technique of controlled ventilation using muscle relaxants. This is because of the significant effect which a low arterial carbon dioxide tension produced in this way has on IOP (Adams and Barnett, 1966; Samuel and Beaugié, 1974). This technique is also particularly suitable for elderly patients with their reduced respiratory reserve and tendency to respiratory depression. However, the resumption of adequate spontaneous respiration after antagonism of residual neuromuscular blockade may be delayed, thereby slowing turnround of patients on a busy operating list.

Many anaesthetists have favoured a technique of spontaneous respiration using nitrous oxide, oxygen, and halothane, because recovery from anaesthesia is prompt (Kaufman, 1967; Adams and Fordham, 1973). However, the disadvantage of this technique is that halothane in inspired concentrations of 1·5 to 2% needs to be given to be sure that the patient does not react during the operation. These concentrations may eventually lead to tachypnoea and shallow breathing, resulting in respiratory acidosis. The effect of a rise in arterial carbon dioxide tension ($PaCO_2$) on IOP is offset to some extent by the effect of halothane (Al-Abrak and Samuel, 1974). However, eventually these doses of halothane may cause profound hypotension in elderly patients. The hypotension is most marked in patients who have essential hypertension and who are not receiving medical treatment (Prys-Roberts *et al.*, 1971). This problem hardly ever arose when the Graefe knife was in vogue, as the time of operation was so short. However, most intraocular surgery now takes longer because of the use of the operating microscope and more elaborate suturing techniques. These advances have highlighted the deficiencies of the spontaneous breathing anaesthetic technique.

This paper considers the effects on intraocular pressure of a simple standardised technique by means of muscle relaxants and controlled ventilation at normocapnia with the recently-introduced Bain coaxial circuit (Bain and Spoerel, 1972; Henville and Adams, 1976a). This circuit is a coaxial form of the Mapleson D/E type breathing circuit, which

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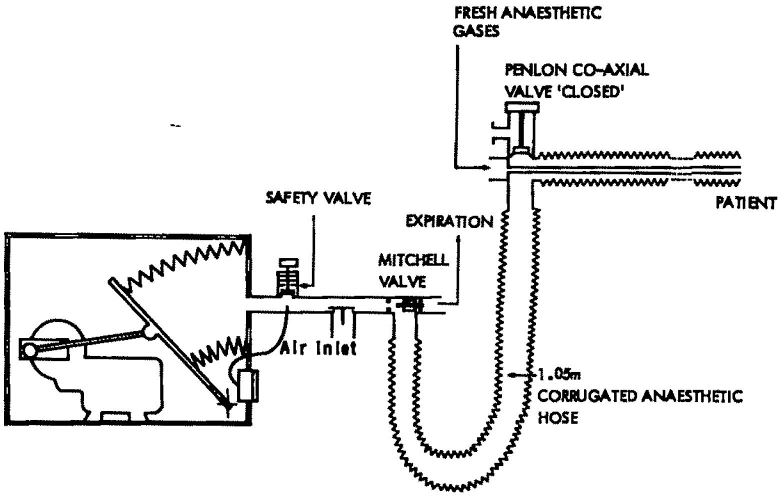

Fig. 1 *Circuit diagram of coaxial anaesthetic breathing circuit connected to Cape Minor lung ventillator*

through controlled rebreathing maintains the PCO_2 at a level determined by the flow of fresh gas into the circuit (Fig. 1).

Patients and methods

PATIENTS

Twenty-three patients with cataracts were admitted for lens extraction under general anaesthesia. There were 12 males and 11 females. Their mean age was 72 years (range 37 to 88 years) and mean weight 65·3 kg (range 39 to 101·4 kg). The anaesthetist saw all the patients preoperatively and assessed their fitness. No attempt was made to select patients other than to exclude those who either were untreated hypertensives whose diastolic pressure was greater than 110 mmHg or were in gross congestive cardiac failure. Several patients were taking medication in the form of digoxin, antihypertensive drugs, diuretics, potassium supplements, oral hypoglycaemic drugs, mild analgesics and night sedatives, or tranquillisers.

MEASUREMENTS OF IOP

When the patients arrived in the anaesthetic room the cornea of both eyes was anaesthetised by the application of 1 to 2 drops of 0·5% proxymetacaine (Ophthaine) solution. Fluorescein was then applied from dye-impregnated paper strips, and the IOP was measured by a Perkins hand-held applanation tonometer (Perkins, 1965).

All tonometric measurements were performed by the same person (A.F.) Further IOP measurements were made in both eyes 10 minutes after the initial readings had been obtained, which was after full general anaesthesia had been established with controlled ventilation of the lungs. Tonometry was also performed on the non-operated eye both at the conclusion of surgery while the general anaesthetic was maintained and immediately after spontaneous breathing had been re-established following withdrawal of the anaesthetic gases and the antagonism of residual neuromuscular block. Difficulties in obtaining a clear end-point with the tonometer at this time due to the uptake of fluorescein by the cornea occurred in 3 patients. These patients have been excluded from the study.

ANAESTHESIA

All patients were premedicated with 0·6 mg atropine given intramuscularly about 1 hour before surgery. This is not believed to have any effect on IOP. Induction of anaesthesia is likely to be accompanied by a rise of IOP because of the administration of suxamethonium followed by tracheal intubation (Taylor *et al.*, 1968; Pandey *et al.*, 1972). General anaesthesia was induced with intravenous thiopentone 4 to 5 mg/kg followed immediately by suxamethonium 1·5 mg/kg; this large dose of suxamethonium helps to permit easy tracheal intubation under profound paralysis with no reaction from the patient and minimises the rise in IOP.

The extraocular muscles have been shown to exhibit a biphasic response to suxamethonium on account of their possession of two types of muscle fibre: tonic, multi-inverted fibres which respond only to tetanic stimuli with a slow contraction, and phasic, singly innervated fibres which respond with a twitch to a single stimulus. A dose of suxamethonium which relaxes skeletal muscle may produce a tonic contracture of the extraocular muscles, squeezing the eyeball and producing a transient rise in IOP (Gibb, 1974; Wislicki, 1976). If, however, a sufficiently large dose of suxamethonium is given, relaxation of both types of muscle fibre is produced (Joshi and Bruce, 1975).

Laryngoscopy was performed after inflation of the lungs with oxygen. The vocal cords and trachea were sprayed with 1 to 2 ml 4% lignocaine, and the trachea was intubated with size 8 to 9 Oxford pattern non-kinking cuffed endotracheal tube (Duckworth, 1962).

VENTILATION

Ventilation was controlled initially by hand, a mixture of 33% oxygen, and 0·5% halothane in nitrous oxide being delivered from a Bain anaesthetic breathing circuit. The purpose of the halothane was to ensure unconsciousness during the operation while permitting an adequate concentration of inspired oxygen in this elderly group of patients, and also to reduce the IOP. The fresh-gas flow from the anaesthetic machine was adjusted to give a total flow ($\dot{V}_f$) as close to 70 ml/kg per minute as possible so as to obtain normocapnia during the operation (Bain and Spoerel, 1973; Henville and Adams, 1976b). The anaeshetic machine used was a British Oxygen Company Boyle's machine model E; the etchings on the Rotameter tubes of this old machine permitted a more exact setting of fresh gas flows than is possible with the new 'long-range' double-tapered tubes provided on more modern machines.

Gallamine triethiodide (Flaxedil) in a dose of 2 mg/kg, but not exceeding 120 mg in a single dose, was then given intravenously to permit synchronisation with an automatic lung ventilator which provided intermittent positive pressure ventilation (IPPV) of the lungs throughout the operation. It must be emphasised that this dose is insufficient to permit tracheal intubation without the patient's reacting. Gallamine was chosen because of its short duration of action and lack of serious side effects. The tachycardia induced by the drug caused no problems; in particular bleeding was not exaggerated.

Electrically powered anaesthetic ventilators were used for convenience, as medical gas supplies from pipelines were unavailable. Two types of machine were used. (*a*) A British Oxygen Company Mark 4 Beaver ventilator was used on 21 patients. This machine is a pressure preset machine (Mushin *et al.*, 1969); the 'over-pressure' relief valve had been modified in the anaesthetic workshop to allow slightly higher peak inflating pressures to be used than the 30 cmH$_2$O originally permitted. (*b*) A Cape Minor Ventilator, which is a volume-preset machine (Collis, 1967), was used on the remaining 2 patients. Both these ventilators delivered room air into the Bain anaesthetic system. The interposition of a 1·05-m length of standard anaesthetic corrugated breathing hose (22 m diameter) between the ventilator and the beginning of the outer limb of the Bain circuit ensured that the air did not enter the patients' lungs (Adams, 1977a).

In order to keep mean intrathoracic pressure low during such IPPV and to maintain optimal ventilation of the lungs during anaesthesia the tidal volume was adjusted to about 10 ml/kg with a slow respiratory frequency. However, the Cape Minor machine had a slight disadvantage because its frequency could not be reduced from the fixed rate of 16 cycles/minute. Expired minute volumes and tidal volumes were checked by inserting an electronic Wright's respirometer (Conway *et al.*, 1974) (BOC-Medishield Ltd.) between the catheter mount and the Bain circuit. Although the additional dead-space introduced was only about 22 ml, the instrument was removed when the desired ventilation had been achieved and before the operation began. A repeat check of the ventilation was performed at the end of surgery.

Ventilation was continued throughout the operation, which lasted 30 to 40 minutes on average. It was not found necessary to give any further muscle relaxant. Half-way through the operation 10 mg of metoclopramide was given intramuscularly as a prophylactic against sickness in the postoperative period.

In the concluding phase of the operation arterial blood was sampled from the radial artery. The 2-ml syringes containing blood samples were transported in iced water to the blood-gas laboratory where analysis was performed within 45 minutes with Radiometer PO$_2$, PCO$_2$, and pH electrodes. Standard corrections were applied to these results for storage time (Kelman and Nunn, 1966). At the end of the operation IOP was measured in the non-operated eye. Residual neuromuscular block was then reversed with 0·6 mg atropine (or 1·2 mg if the tachycardia from the gallamine had worn off) and 2·5 mg neostigmine, the secretions in the pharynx were aspirated, and the endotracheal tube was removed. No problems due to profuse salivation or vomiting followed neostigmine administration. Oxygen was administered through an anaesthetic face mask, care being taken not to press on the eyes, and spontaneous breathing was resumed well within 5 minutes. At this point the IOP was again determined. The patient was then turned on to one side and given oxygen-enriched air to breathe from a plastic disposable MC oxygen mask for a minimum period of 10 minutes, and on regaining complete consciousness was returned to the ward.

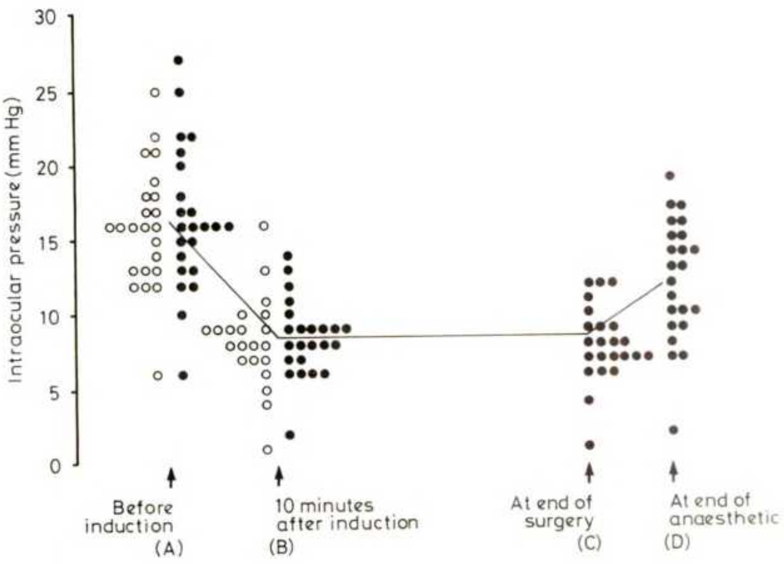

Fig. 2 *Intraocular pressure determined by applanation tonometry at various stages of anaesthesia and surgery*

○ = *Operated eye.*

● = *Non-operated eye.*

— = *Mean IOP*

Results

ANAESTHESIA

The mean total fresh-gas flow ($\dot{V}_f$) set on the anaesthetic flowmeters was 4·7 litres/minute; this corresponded well with the calculated desired requirements for normocapnia of 4·6 litres/minute.

The mean expired minute volume ($\dot{V}_E$) was 9·4 litres/minute, that is, 144 ml/kg per minute, at a mean frequency of ventilation of 13 cycles/minute giving a mean tidal volume of 11 ml/kg.

INTRAOCULAR PRESSURE

The mean intraocular pressure (IOP) measured in the anaesthetic room immediately before the establishment of general anaesthesia was 16·0 mmHg in the eye to be operated upon and 16·5 mmHg in the other eye; this difference was not significant ($t = 0{\cdot}437$). Measurements made 10 minutes after the induction of anaesthesia with the patient in the operating theatre and the surgeon ready to start the operation showed equally marked falls of almost 50% in the IOP in both eyes (Fig. 2 and Table 1). There was no statistical difference between the mean pressure in either eye.

The duration of surgery was 30 to 40 minutes. The mean IOP at the end of surgery was 7·9 mmHg which was not statistically significant from the pressure just before starting the operation. However, the IOP rose to 12·1 mmHg when the anaesthetic was discontinued and spontaneous breathing became re-established. This rise was statistically significant ($P < 0{\cdot}001$) when compared with the IOP at the end of operation. It is likely that the IOP continued to rise, because this final measurement was still significantly less than that obtained preoperatively ($P < 0{\cdot}001$).

ARTERIAL PRESSURE

Systolic arterial pressure fell from a mean preoperative value of 151 mmHg in the anaesthetic room to a mean of 113 mmHg 10 minutes after the induction of anaesthesia. The pressure remained

Table 1 *IOP in 23 patients before, during, and at the end of general anaesthesia. There is no significant difference between the IOP results given for the operated and the non-operated eye. The statistical differences for IOP between the groups gave by Student's* t *$P < 0{\cdot}001$, except that there was no significant difference between groups* B *and* C. *Mean $PaCO_2$ 42·0 mmHg (SE mean 0·98), mean PaO_2 127·6 mmHg (SE mean 4·4)*

	IOP (SE mean) (mmHg)	
	Non-operated eye	*Operated eye*
A Before induction of general anaesthesia (systolic arterial pressure 151 mmHg)	16·5 (1·00)	16·0 (0·85)
B Ten minutes after induction of general anaesthesia (systolic arterial pressure 113 mmHg)	8·4 (0·54)	8·4 (0·61)
C At end of cataract surgery (systolic arterial pressure 112 mmHg)	7·9 (0·54)	—
D After reversal of relaxant drugs, during spontaneous breathing (systolic arterial pressure 126 mmHg)	12·1 (0·84)	—

fairly constant thereafter throughout the operation and rose slightly towards the preoperative value when the residual neuromuscular blockage had been reversed with neostigmine and atropine, the nitrous oxide and halothane had been withdrawn, and spontaneous breathing had become re-established on oxygen (Table 1).

ARTERIAL BLOOD GASES

The mean arterial carbon dioxide tension ($PaCO_2$) of blood taken at the end of surgery, while the patient was still being ventilated, was 42·0 mmHg (SE mean, 0·98 mmHg). The mean arterial oxygen tension (PaO_2) at this time was 127·6 mmHg, the mean arterial pH was 7·374, and the mean base deficit was 0·8 mmol/litre. Because pH is a logarithmic function, the mean pH value stated above was calculated after conversion of the individual pH values into terms of hydrogen ion concentrations.

POSTOPERATIVE PROBLEMS

There were no systemic complications in any of the patients. One patient had a small iris prolapse which did not require repair. Another patient, who was a diabetic, had a persistent hyphaema and a raised IOP, which resolved satisfactorily.

Discussion

General anaesthesia has only slowly become accepted as the method of choice in ophthalmic surgery. The eye can easily be rendered insensitive and immobile by local anaesthetics, and as recently as 1966, this was the method of choice proposed for cataract extraction (Snow and Sensel, 1966).

The chief problem of general anaesthesia has been its unpredictable effect on IOP. This question has engaged the attention of anaesthetists for many years without a completely satisfactory solution, as shown by the wealth of papers claiming superiority for various techniques (Ives, 1959; Burn and Knight, 1969; Jones *et al.*, 1969; Smith *et al.*, 1972; Delilkan and Chandran, 1972; Lynch *et al.*, 1974).

All eye surgeons must have experienced at some time the unnerving complications resulting from a raised IOP during intraocular surgery. Such danger signs as a shallow anterior chamber with iris prolapse on opening the eye, caused by an anterior shift of the lens-iris diaphragm, may be followed by vitreous loss, retinal haemorrhage, and choroidal haemorrhage which may be so massive as to take the form of that major disaster, an expulsive haemorrhage (Ruiz and Salmonsen, 1976).

The progress of general anaesthesia in recent years is illustrated by the figures from the Oxford Eye Hospital. In 1965 57% of all operations were performed under local anaesthesia; by 1971 the proportion had fallen to 20%. The figures for cataract extraction are even more striking, for, while in 1965 97% of these procedures were done under local anaesthesia, in 1971 the figure had fallen to 13·5%. Similarly, of 1133 cataract extractions performed at Moorfields Eye Hospital, London, in 1974–75 only 4·6% were performed under local anaesthesia. Many of the mechanisms which cause a change in intracranial pressure have a similar effect on IOP.

The importance of giving a large dose of suxamethonium to facilitate endotracheal intubation has already been mentioned. Contracture of extraocular muscle is not the only effect of suxamethonium, as section of the muscles does not completely abolish the rise in IOP (Craythorne *et al.*, 1960; Adams and Barnett, 1966). Suxamethonium probably increases the blood flow in the choroid, resulting in raised blood volume and increased IOP (Wahlin, 1960; Adams and Barnett, 1966; Wilson *et al.*, 1974). This rise in IOP cannot be prevented entirely by prior administration of small doses of pancuronium (Miller *et al.*, 1968; Bowen *et al.*, 1976). The administration of even a large dose of suxamethonium still poses a problem in patients with penetrating eye injuries, since a rise in IOP may result in a loss of ocular contents. Its administration in these circumstances should be avoided unless doing so would expose the patient to greater hazard. It has been shown that acetazolamide increases choroidal blood flow by up to three times. This drug has previously been claimed to prevent suxamethonium-induced rise of intraocular pressure, though the mechanism is obscure (Carballo, 1965). It seems likely that acetazolamide may in fact produce an increase in IOP itself, after which the effect of suxamethonium is attenuated (Holloway, 1977). Suxamethonium similarly produces no further pressure rise in eyes in which the tension is already high, and there is therefore no contraindication to its use in glaucoma and related conditions.

Non-depolarising muscle relaxants generally have only a small effect on IOP consequent upon the relaxation of the extraocular muscles and the orbicularis oculi (Duncalf and Foldes, 1973; Eriksen *et al.*, 1977). Tubocurarine may have a greater effect because of its hypotensive activity.

A rise in systemic arterial pressure does not produce a rise in IOP as vessels constrict and blood flow diminishes. A fall in arterial pressure below normal levels does, however, produce a concomitant and progressive fall in IOP. Any drug or technique which produces a fall in arterial pressure will therefore be effective in lowering IOP (Scullica *et al.*, 1973). The ganglion-blocking agents have been previously used for this purpose, although few would now consider such use to be indicated for ophthalmic surgery.

The central venous pressure has an important effect on IOP, as any rise interferes with the venous outflow and aqueous drainage from the eye, resulting in a rise of IOP. Hence it is important to prevent coughing, vomiting, and straining.

Arterial carbon dioxide tension has been shown to be a potent determinant of IOP, probably by altering blood flow through the choroid and retrobulbar vessels. IOP varies directly with CO_2 tension within a fairly wide range of values.

Intravenous and inhalational anaesthetic agents promote a fall in IOP, which generally increases with increasing depth of anaesthesia. The administration of an adequate dose of thiopentone immediately before giving suxamethonium to some extent reduces the rise in IOP which would otherwise be caused by a first dose of suxamethonium. The action of halothane in lowering IOP is in contrast to its effect on intracranial pressure. Ketamine and trichloroethylene are the exceptions in this group of drugs; their administration is followed by a slight rise in IOP (Yoshikawa and Murai, 1971; Al Abrak and Samuel, 1975). However, claims that ketamine is not associated with any increase in IOP should be viewed with some suspicion, because pretreatment with diazepam (Peuler *et al.*, 1975) or pethidine (Ausinsch *et al.*, 1976) may be responsible.

From the foregoing considerations it is clear that many drugs and techniques permit the intraocular tension to be actively lowered or at least prevented from rising, and a suitably soft eye for intraocular surgery can be produced by a combination of methods.

Most patients requiring cataract extraction are elderly and are therefore likely to suffer from cardiovascular and respiratory dysfunction. With spontaneous respiration during anaesthesia, such patients commonly hypoventilate, with consequent development of hypercapnia, hypoxia, and reduction of functional residual capacity, increasing the risk of postoperative pulmonary collapse and infection. There are also disadvantages in artificial ventilation with the production of hypocapnia: cardiac output is reduced (Prys-Roberts *et al.*, 1967), and depletion of carbon dioxide stores means that postoperative hypoventilation with hypoxaemia is inevitable (Salvatore *et al.*, 1969).

For these reasons a technique for cataract surgery which produces a significant fall in IOP while maintaining a near-normal arterial carbon dioxide tension together with adequate ventilation and oxygenation appears desirable. This is achieved by controlled ventilation with a partial rebreathing circuit such as the Bain circuit. The circuit is particularly appropriate for head and neck surgery as it is light in weight, of a suitable length (2 m), and has its valve and connections well away from the patient. Anaesthesia with a nitrous oxide and oxygen mixture containing 0·5% halothane and controlled ventilation following administration of a non-depolarising muscle relaxant, after induction as described above, produced the required operating conditions for intraocular surgery: the mean intraoperative IOP was 52% of the preanaesthetic level.

This technique has several advantages for intraocular surgery in elderly patients. Muscle relaxation prevents the possibility of straining or coughing during the operation. Oxygenation and adequate lung inflation are ensured by hyperventilation without hypocapnia. The technique ensures a soft eye even when preoperative IOP is high. In many cases an air bubble was spontaneously retained in the anterior chamber when the eye was opened. The return of adequate spontaneous ventilation is achieved promptly after reversal, making it suitable for relatively short (½ to ¾ hour) cases, and recovery of protective reflexes and consciousness is rapid.

Addendum.—The Beaver ventilator is no longer manufactured. The Cape Minor has proved to be so successful as an inexpensive and simple electrically-powered ventilator for use with the Bain circuit that the manufacturers (Cape Engineering Co., Warwick) now produce a much improved version, the Cape TC50. This new machine permits an infinitely variable frequency of between 10 and 50 cycles/minute by means of a thyristor-controlled motor (Adams, 1977b). There is an improved preset and directly calibrated tidal volume control, while the important feature of a bellows circuit that can be autoclaved is retained.

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Book reviews

The Ocular and Cerebrospinal Fluids. Edited by L. Z. BITO, H. DAVSON, and J. D. FENSTERMACHER. 1977. Pp. 561, figs., tables, refs. Academic Press, London (£20)

In 1956 Dr Hugh Davson produced a memorable monograph on *The Physiology of the Ocular and Cerebrospinal Fluids*, and by a fortunate concatenation of circumstances he has been able, 20 years later and under the auspices of the Fogarty International Centre, to organise a symposium on the same topics. This symposium, which was held in May 1976, brought together contributions from the many research workers who have intrepidly voyaged into regions which 20 years ago could be referred to as 'backwaters of physiology'. The contributions in this volume show that the backwaters have now become navigable seaways within which many different interests are represented.

The volume contains 40 contributions, of which 18 deal directly with the eye. Most of these are reviews and reports of experimental rather than clinical studies, though the contribution on papilloedema from Cogan and Kuwabara is an obvious exception. Of the review papers those by Raviola (blood-ocular barriers), Tripathi (morphology of outflow systems), Bill (physiology of aqueous drainage), and Langham (pharmacology of aqueous outflow) are especially valuable, and the papers by Bito and Wallenstein on the transport of prostaglandins and by Eakins on the breakdown of the blood-aqueous barrier break new ground and provide excellent introductions to fresh fields of interest. The papers dealing with cerebrospinal fluid and the blood-brain barrier are no less valuable, and one must single out the reviews by Brightman (morphology of blood-brain interfaces), Oldendorf (blood-brain barrier), and Welch (hydrocephalus).

As is always the case with papers provided at a symposium, the quality of the contributions is not uniformly high. Some have been added in reply to others presented at the meeting and, while valuable in their content, will prove difficult reading for the uninitiated.

The editors might have attempted to make a rather more logical arrangement of their subject-matter; excellent as the contents are for the cognoscenti, they will prove hard going for the tyro. Nevertheless, I believe that this 'Fogarty Symposium' will be an invaluable source of useful information and ideas for many years to come.

DAVID F. COLE

Ocular Therapeutics and Pharmacology. 5th edn. By PHILIP P. ELLIS. 1977. Pp. 283, tables, refs. Mosby, St. Louis (£15·60)

This textbook has undergone an extensive revision in its fifth edition, and new chapters on carbonic anhydrase inhibitors and local anaesthetics have been added. The aim of the book is to provide, firstly, a quick reference to treatment, both medical and surgical, of specific disorders, and secondly to give the usage, dosage, and side-effects of the drugs used in ophthalmology. It is a useful reference book for an ophthalmic library, although the less experienced eye surgeon may at times be confused by the number of therapeutic possibilities which are suggested.

J. H. DOBREE

Correspondence

Pathogenesis of optic disc swelling

TO THE EDITOR, *British Journal of Ophthalmology*

SIR, Your editorial on 'Pathogenesis of Optic Disc Swelling' (September 1978, pp. 579–580) makes the all too common mistake of equating swelling of the disc from ischaemia and similar causes, wherein there is undoubted blockage of axonal transport, with papilloedema from raised intracranial pressure (ICP), wherein at least in the early stages any such blockage is questionable and should be questioned. I am assured, by Tso himself at the 1976 Cambridge symposium, that blockage of axonal flow is not consistent with continuance of normal function. One feature of papilloedema from raised ICP is that normal vision usually continues without interference, apart from variable enlargement of the blind spot, for many weeks or months. I watched 1 case for 5 months who kept normal vision to the end and whose discs on ophthalmoscopy showed nothing suggestive of axonal transport blockage (Primrose, 1976). Prolonged or severe cases may indeed show some suggestive signs on and around the disc, and one would expect these to be cases with some interference with vision, e.g., peripheral constriction of the fields or obscurations, which are both probably from vascular insufficiency and a warning that further severe visual failure is imminent.

Blockage of axonal transport is all very well for the 'final common pathway' but it just won't do for the early stages of papilloedema. The site of such blockage is understandably similar to that found in experimental acute glaucoma and hypotony (Tso and Hayreh, 1977) and posterior ciliary artery occlusion (McLeod, 1976), but how can this be a cause or an early sign in papilloedema from raised ICP when vision is so conspicuously unaffected? These disturbances upset the hydrodynamic balance at a site susceptible for anatomical reasons to vascular insufficiency, and it is surely anoxia from this which causes the blockage. Hayreh's idea (Hayreh, 1977) seems to be that raised retrolaminar tissue pressure from the raised ICP causes some blockage of axonal transport which, from the nerve swelling at the tight hole at Bruch's level, leads to pressure on the thin-walled veins, thus explaining away the venous (and other) congestion so consistently found. A continuing CSF pressure of 300 to 400 mm H_2O (22 to 29 mmHg) seems to be sufficient to produce papilloedema, and a tissue pressure of that level does not damage other nervous tissue (Hayreh, 1977). It doesn't seem to me sufficient by itself to impair axonal flow.

One must seek other reasons for the particular susceptibility of the disc, and the vascular hypothesis, which your editorial ignores, offers a means of explaining both the early engorgement with normal function and a reason for axonal blockage when it does occur. The retrolaminar tissue suffers a reduction of blood flow from shunting to the prelaminar tissue, which shares its blood supply. It would be the first part to suffer from stasis anoxia when things become severe (Primrose, 1976).

Minkler *et al.* (1978) are quoted as favouring a mechanical cause. Yet they at least discuss a vascular cause and think to exclude it only because the central part of the nerve being furthest from the ciliary supply is spared.

A very different interpretation is possible. The retrolaminar tissue supplied by ciliary arteries is deprived by steal; the fine vessels are not empty but the flow is greatly reduced. But the axial part of the retrolaminar tissue receives some supply from the central retinal artery which is not subject to steal, hence this part with its related central field is not so susceptible (Primrose, in press). These authors, and others, would have us believe that the papilloedema produced by hypotony, after cryotherapy sufficient sometimes to produce hyphaema, is the same as that of raised ICP. Their finding of infimmatory cells in the oedematous disc is one indication that it is not the same. Also where in all this experimental work are there any tests to show good visual function? Even if acuity tests are not possible in animals some note of the briskness or otherwise of the pupillary reactions would be of value.

Of course there are mixed cases wherein there is papilloedema as well as axonal blockage. I've seen it myself, and the vision has been impaired. It is most evident clinically in cases of accelerated hypertension in which vision is commonly impaired to some degree and there is a recognised element of ischaemia from patchy small-vessel occlusion (Ashton, 1972). One hopes this letter makes good some of the deficiencies of the editorial and helps to give a more balanced view.

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SIR, Three crucial issues have been raised by Mr Primrose regarding optic disc swelling from raised intracranial pressure.

(i) *Is obstruction of axoplasmic transport compatible with continuing axolemmal conduction of nerve impulses?* Axoplasmic transport and axolemmal conduction are both completely interrupted by localised destruction or ischaemic dissolution of an axon. However, the transport and conduction functions of axons are distinct processes, and there is abundant evidence to suggest that axolemmal conduction can continue along an axon subjected to a *partial* bloackage of axoplasmic transport, e.g., in retinal ganglion cell axons after raising the intraocular pressure (Anderson and Henderickson, 1974). The partial obstruction of axoplasmic transport postulated in clinical papilloedema and demonstrated in experimental papilloedema (Tso and Hayreh, 1977a) is thus compatible with continuing visual function. Nevertheless, how long an axon can survive and continue to conduct action potentials in the face of a partial axoplasmic transport block remains to be established.

Observation of the behaviour of many of the animals with implanted intracranial balloons (Hayreh, 1977a) suggested that their vision was not markedly impaired; however, although visual evoked responses were recorded in 1 animal, more detailed electrophysiological testing would have been valuable. Conversely, detailed psychophysical testing of *patients* with papilloedema may reveal a variety of functional alterations which are not detected on visual acuity and routine visual field testing.

(ii) *Is early papilloedema associated with obstruction of axoplasmic transport?*
Hayreh has repeatedly stressed (Hayreh and Hayreh, 1977a; Hayreh, 1977a) that the disc swelling produced in his experimental model is equivalent to early or moderate papilloedema as seen clinically. Even in early experimental papilloedema the principal cause of disc swelling is distension of axons (as opposed to interstitial oedema), and these histological findings correlate with the ophthalmoscopic and angiographic picture (Tso and Hayreh, 1977b; Hayreh and Hayreh, 1977a). However, although partial obstruction of rapid and slow axoplasmic transport was clearly demonstrated in these animals (Tso and Hayreh, 1977a), no observations relating the severity of the transport block (as demonstrated autoradiographically) to the stage or severity of the disc swelling were made.

Comparison of the ophthalmoscopic appearance of the disc in early papilloedema with that in conditions which Mr Primrose concedes involves an axoplasmic transport block (e.g., ischaemic optic neuropathy) supports the concept that similar pathophysiological mechanisms are operating in the prelaminar region.

(iii) *What is the cause of the axoplasmic transport block in papilloedema?*
Hayreh (1977b) has speculated that the cause of the laminar transport block is *mechanical* (from transmission of raised intracranial pressure to retinal ganglion cell axons in the optic nerve), whereas visual loss in chronic papilloedema results from *prelaminar ischaemia* secondary to the mechanically induced optic disc swelling (Hayreh,

1977a). Neither of these assertions, however, is based on definite evidence. The relevance, for example, of the observation (Hayreh, 1976, 1977b) that fluorescein can diffuse from the cisterna magna to the vitreous cavity via the subarachnoid space, optic nerve, and optic disc is unclear.

The prelaminar venular congestion mentioned by Mr Primrose was observed to be a *late* event during the development of experimental papilloedema (Hayreh and Hayreh, 1977b). Nevertheless, this in no way detracts from the possibility that an ischaemic mechanism may be operating in the *retrolaminar* ciliary artery territory (as postulated, though unsubstantiated, by Mr Primrose) and may be contributing to the axoplasmic transport block in papilloedema. DAVID MCLEOD

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Early postoperative sterile hypopyons

SIR, The article by Hunter (1978) mentions a high incidence of hypopyons following lens extraction and describes them as being sterile. The physiological reasons presented by the author explaining these hypopyons may be correct, but the possibility of infection is not mentioned.

The minimum infective dose even for virulent staphylococci is much greater than hitherto thought (Elek, 1959). That the actual number of bacteria implanted in an eye is an important factor was proved by Maylath and Leopold (1955), who injected into the cornea, anterior chamber, and vitreous of rabbits' eyes varying doses of different species of pathogenic bacteria. Their work was confirmed by Crompton *et al.* (1962) who assessed the virulence of small doses of several species injected intracamerally. In untreated rabbits, depending on the dose and species of bacteria used, a graded response is produced from no reaction to a transient hypopyon or panophthalmitis with destruction of the eye.

Maylath and Leopold (1955) found that positive cultures of intraocular infections were difficult to obtain in rabbits, and this was confirmed (Crompton *et al.*, 1962). All ophthalmologists must be aware of the difficulty in culturing organisms from the anterior chamber of patients with panophthalmitis. Hunter (1978) assumes that the hypopyons he described are sterile. A likely cause in some of these patients would be small doses of virulent bacteria or larger doses of nonpathogens. It would be unfortunate if this interesting paper encouraged complacency in aseptic technique. D. O. CROMPTON

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SIR, While I appreciate Mr Crompton's concern over the maintenance of the highest standards of aseptic technique, I do not consider that my article (Hunter, 1978) endangers these standards.

In the introduction to this article it is stated that the initial reaction was to investigate and treat these hypopyons as being of infective origin, and, additionally, the operating theatre was closed on the first two occasions. However, no organism was cultured nor was any source of potential contamination found, this despite a total of 5 hypopyons in the first and 3 in the second affected lists (Theodore (1965) considered that *Pseudomonas aeruginosa* was the infectious agent in all known instances of multiple infection). Other major centres in England had also noted an apparent increase in early postoperative hypopyons, but none considered them by investigation results, presentation, or behaviour to be infective in type.

Forster *et al.* (1978) obtained positive cultures from 50% of vitreous and to a lesser extent anterior chamber aspirates in endophthalmitis, but it was considered clinically unjustified to proceed with these aspirations during the series described, as in all other respects these were routine quiet postoperative eyes. In particular there was no lid oedema, chemosis, or loss of anterior chamber or corneal clarity (Fasanella, 1957; Theodore, 1978; Peyman *et al.*, 1978), no undue pain, and the hypopyons were well established by 24 hours (Allen and

Grove, 1976). The eyes surveyed showed no difference in behaviour whether with or without hypopyons, and only 7% of the actual hypopyon incidence was found by the firms treating the patients, partly because of the unremarkable appearance and behaviour of the eyes. Additionally, only routine postoperative treatment with prednisolone with neomycin 0·5% drops 3 times a day and atropine 1% drops 3 times a day was given, yet all but a few resolved in from 2 to 4 days. Allen and Grove (1976); Allen (1978); and Christy and Lall (1973) stress the poor visual outcome in endophthalmitis, Allen (1978) finding only a 10% incidence of better than 6/60 vision, while Peyman *et al.* (1978) achieved only 46% better than 6/60 vision despite the use of intravitreal antibiotics or vitrectomy. None of the patients in the series I described suffered any untoward sequelae, and in particular the visual outcome was normal, taking into account the state of the macula, etc. Forster (1974) believed that sterile inflammation was present in most cases when vitreous and anterior chamber aspirate cultures were negative, finding the commonly reported high incidence of visual loss in positive cultures, but an 88·9% retention of useful vision in those recent postoperative cases with negative cultures. The visual outcome in my series would appear to fit Forster's sterile inflammation group.

While I cannot deny the possibility that some of the hypopyons described were a reaction to organisms, none behaved as infected eyes, so that the term sterile was used partly to denote the benign nature of the outcome in these cases, and the results were published to draw attention to the high incidence of aseptic hypopyons with current surgical techniques.

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Notes

Vitrectomy symposium

A symposium on vitrectomy microsurgery will be held on 18 April 1979 at the Hyatt Regency Hotel in San Francisco, and it will be followed by 2 days of workshop sessions on vitrectomy techniques for the anterior segment surgeon. The symposium is designed to provide current thinking on the indications, techniques, and results of vitrectomy instrumentation in a variety of anterior and posterior segment eye diseases. Further information from: Extended Programs in Medical Education, Room 569-U, University of California, San Francisco, California 94143, USA.

Microsurgery course

The Department of Clinical Ophthalmology of the Institute of Ophthalmology will be conducting a course in Ophthalmic Microsurgery on 2–4 May 1979. It will be a practical course concerning common intraocular surgical procedures. Fees for the Course will be £80·00, and the *closing date for applications is 20 March 1979.* Application forms and further details may be obtained from Mrs P. M. Usher, Microsurgical Course Secretary, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD.

Irish Ophthalmological Society

The Annual Meeting will be held in Cork on 24–25 May. Details from Dr J. G. Madden, 21 St Patrick's Hill, Cork, Ireland.

Electrophysiology of vision

The International Society for Clinical Electrophysiology of Vision will hold its 17th Symposium in Schloss Reinhardsbrunn, Friedrichroda, German Democratic Republic, on 5–10 June 1979. Two topics have been selected: 'Visual electrodiagnosis in systemic diseases' and 'Visual electrophysiology and localised retinal stimulation'. The official language of the symposium is English. Further information from Professor Dr E. Schmöger, Augenklinik der Medizinische Akademie, Nordhäuserstr. 74, 50 Erfurt, GDR.

Scanning electron microscopy

An international meeting on scanning electron microscopy in ophthalmology will be held at Brest, France, on 22 June 1979. Languages French and English. Speakers to submit abstracts by 31 March. Details from Dr J. Colin, Service d'Ophtalmologie, Centre Hospitalier Régional, 29279 Brest Cedex, France.

Canadian meeting

The 42nd Annual Meeting of the Canadian Ophthalmological Society will be held in Toronto on 24–27 June 1979. Further details from PO Box 8844, Ottawa, Ontario, Canada K1G 3G2.

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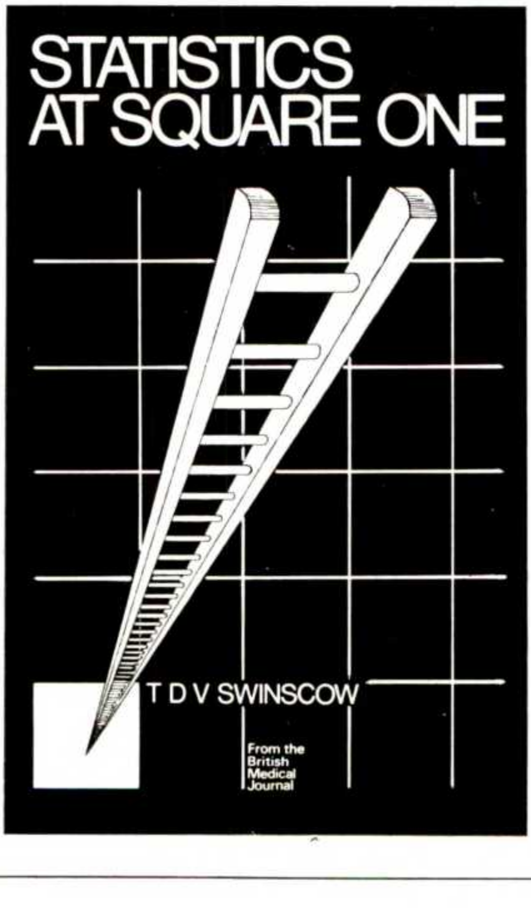

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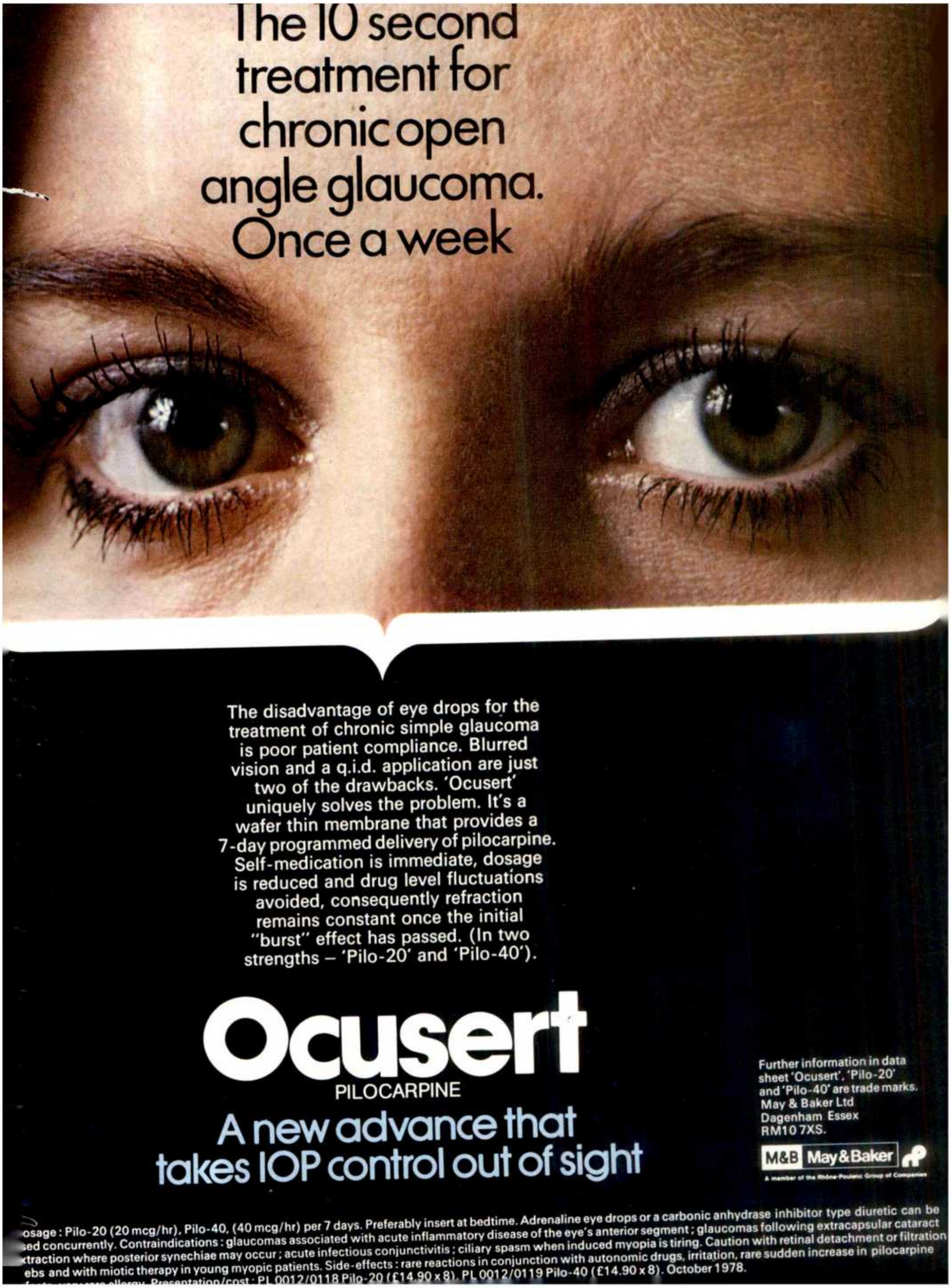

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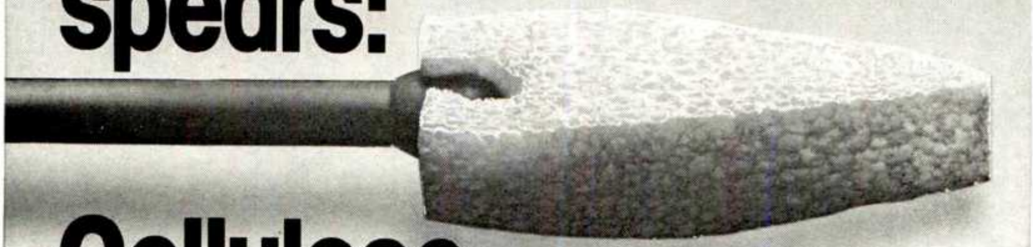

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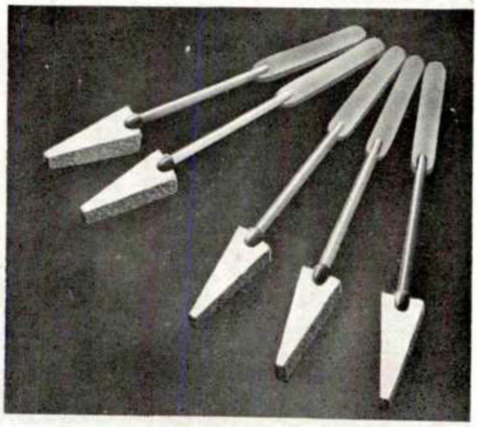

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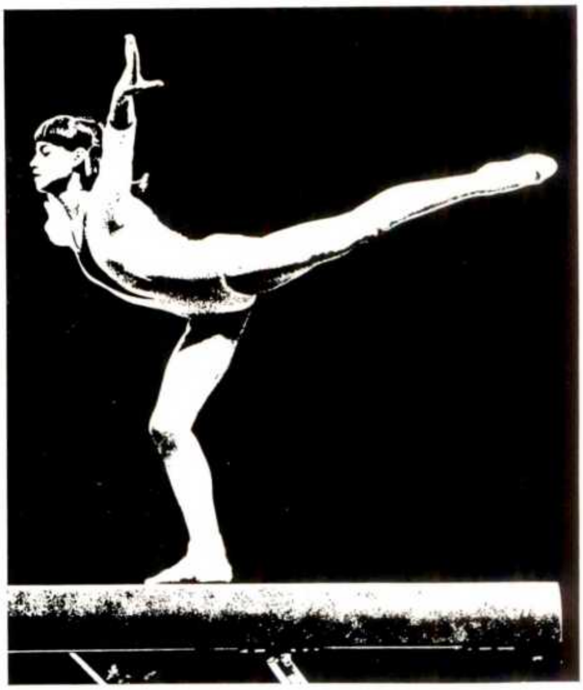

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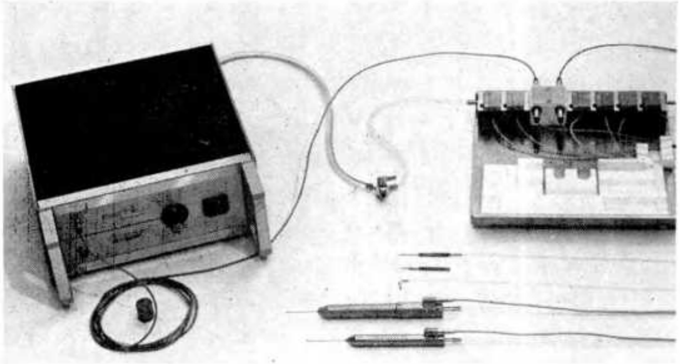

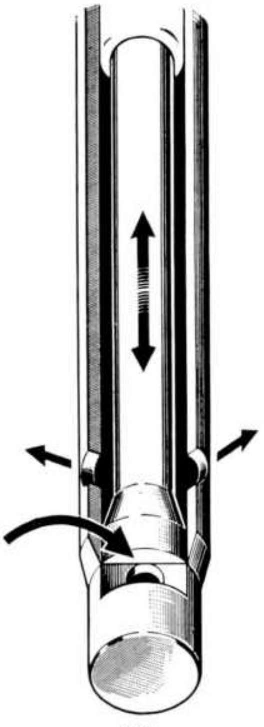

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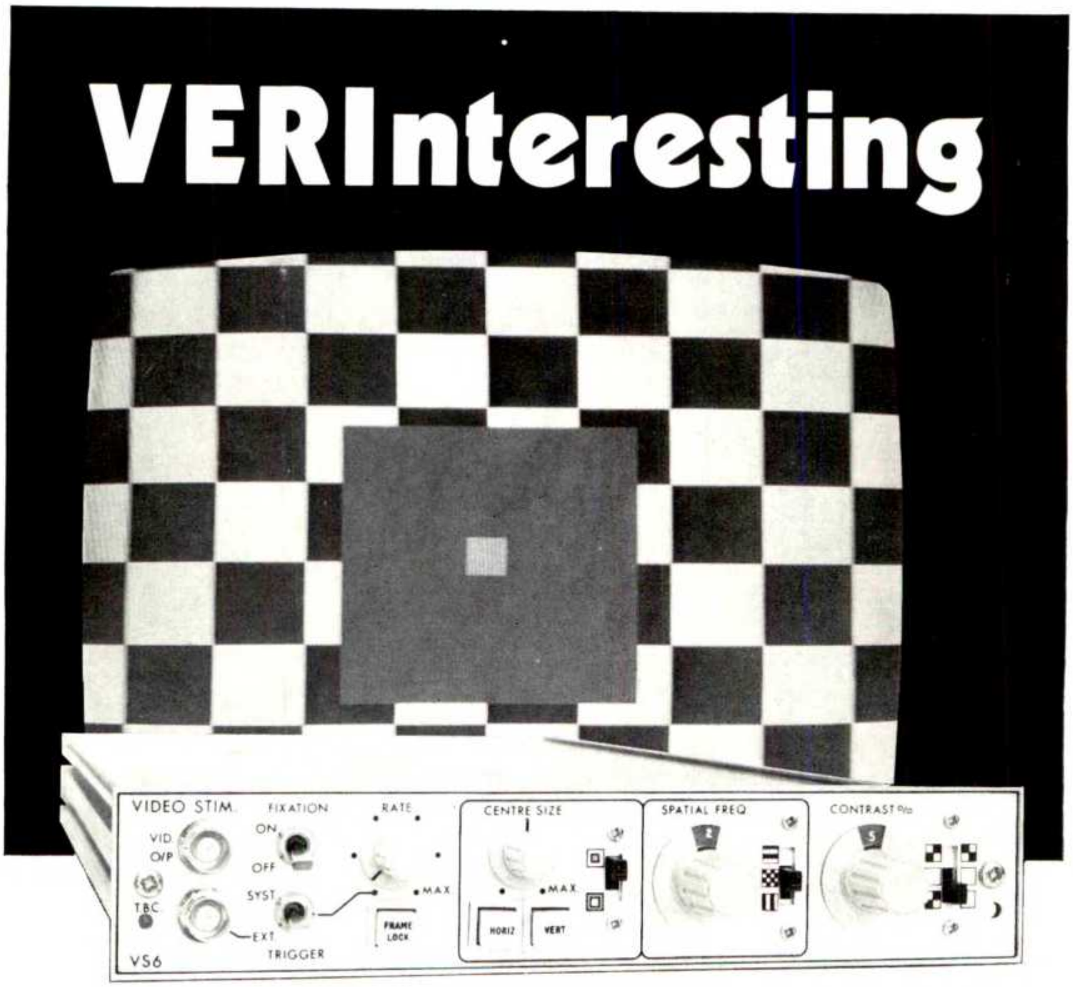

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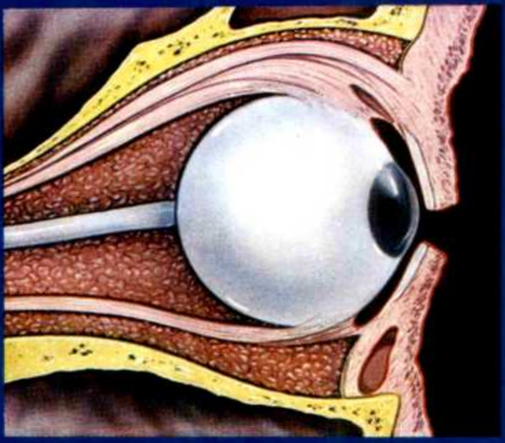

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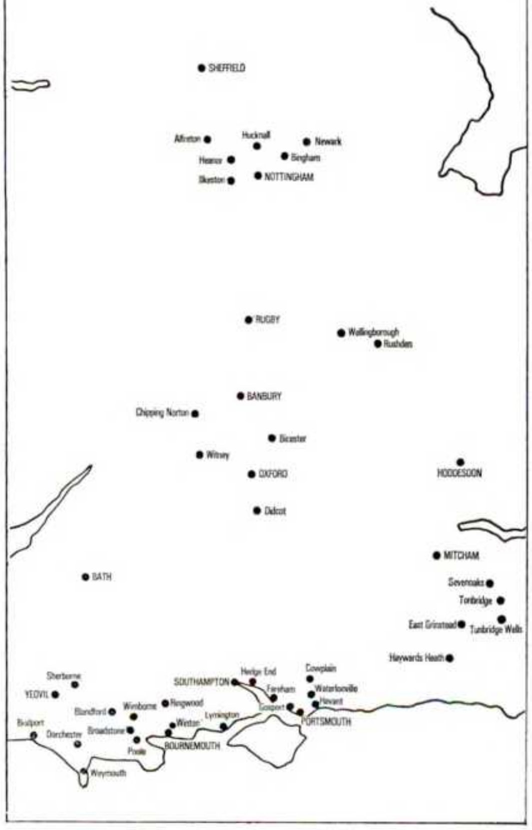

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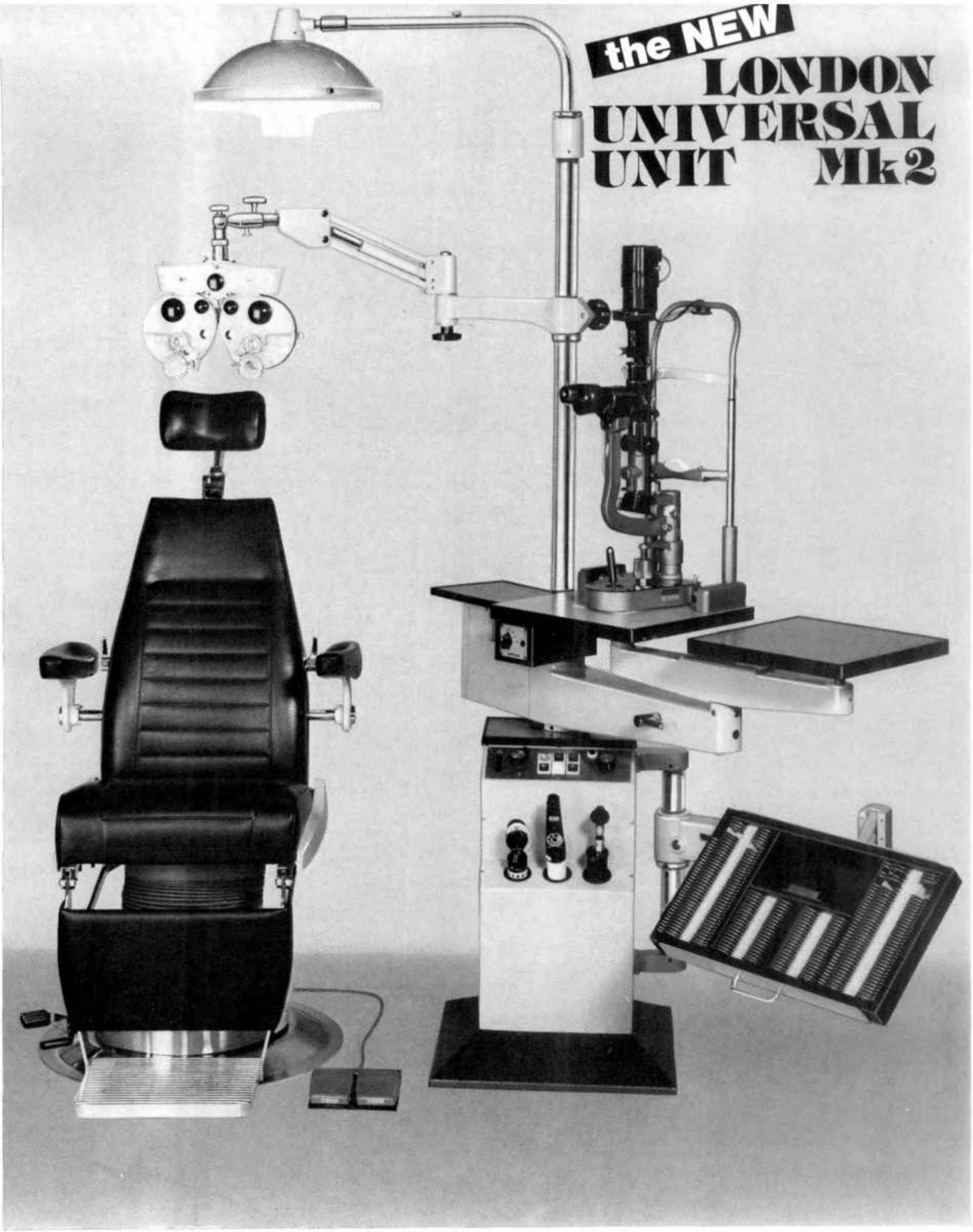

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British Journal of Ophthalmology, 1979, **63**, 215–220

A new method of estimating the depth of the anterior chamber

REDMOND J. H. SMITH

From Moorfields Eye Hospital and the Western Ophthalmic Hospital, London

SUMMARY A new method of estimating the depth of the anterior chamber with an accuracy of approximately 0·1 mm is described. The estimate is made with a conventional Haag-Streit 900 slit lamp without any extra attachments.

Measurement of the depth of the anterior chamber can be carried out under clinical conditions by means of the attachment to the Haag-Streit 900 slit lamp, which is based on the method of Jaeger (1952). Photographic measurements can be made as described by Heim (1941), Bleeker (1960, 1961), and Brown (1973), and ultrasonic techniques can also be used.

An ingenious optical device embodying 2 pairs of apertures, each providing independently focusing double pencils—1 pair to be coincident on the corneal endothelium and 1 on the lens capsule—was described by Stenstrom (1953) as a modification of a device invented by Lindstedt (1916). All these methods, however, require the use of special attachments to the slit lamp, with or without photographic techniques in addition.

The method to be described uses the standard model Haag-Streit 900 slit lamp alone; no extra apparatus is required.

Technique

The slit-beam rotating device is pushed fully to the right so that the slit is horizontal. The angle between the slit beam and the microscope is set at 60° and locked (Fig. 1). For measurement on the right eye the apparatus is arranged so that the slit beam is on the operator's left (the patient's right) and *vice versa* for the other eye. The right eyepiece is used for the right eye and the left for the left eye.

The microscope is aimed so that it is pointing straight ahead, that is, in the optical axis of the patient, and the patient is asked to look straight ahead. The apparatus is moved forward by means of the joystick until the slit beam is focused on the cornea.

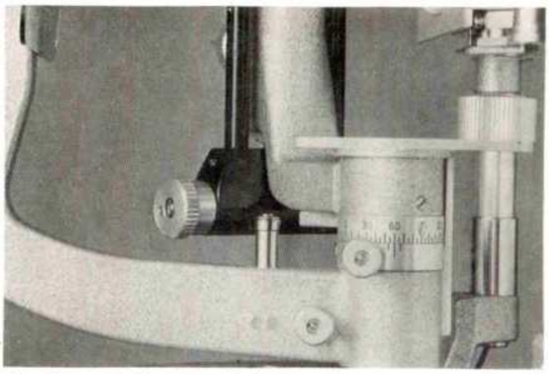

Fig. 1 *Angle between slit lamp and microscope set at 60°*

The thickness of the slit is not vitally important. Preferably a fairly solid beam is used, not a wafer-thin slit, and the technique is slightly easier if the tear film is lightly stained with fluorescein as in applanation tonometry. The length of the slit used can be read on the scale situated on the upper part of the lamp housing (Fig. 2).

The right-hand edge of the slit beam is carefully observed, and the slit beam is altered in length by the knurled knob provided. When the slit is long the picture obtained is as follows: To the left is the sharply focused slit image on the cornea. As one looks along this to the right, the image suddenly becomes more blurred; the blurred zone is the out-of-focus slit image on the anterior lens capsule and, depending on the size of the pupil, more to the right on the iris.

If the slit is considerably shortened, the picture viewed from left to right is as follows: The left end of the slit image is light green owing to the tear film.

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Immediately to the right of this and continuous with the green band the strip is white as it traverses the corneal stroma. Next there is an optically empty gap until the out-of-focus slit image on the lens and iris is reached (position *A*, Fig. 3). The slit is now lengthened until the gap is just obliterated. At this moment the optical conditions are such that the right-hand edge of the slit image on the cornea (at endothelial level) is coincident with the left-hand edge of the slit image at the anterior lens surface (position *B*, Fig. 4).

A simplified optical diagram of the condition is shown (Fig. 5). The true optical diagram would be much more complicated owing to refractive deviation of the slit beam, but for descriptive purposes at this stage the simplified diagram will suffice.

Considering Fig. 5:

$BC_1\ B_1$ is the path of the left edge of the beam,
$AC\ A_1$ is the path of the right edge of the beam,
CC_1 is the slit length.

The anterior chamber depth is the side, CB_1, of the triangle, $C\ C_1\ B_1$, of which 1 side is known (CC_1) and angle CB_1C_1 is also known ($= 60°$).

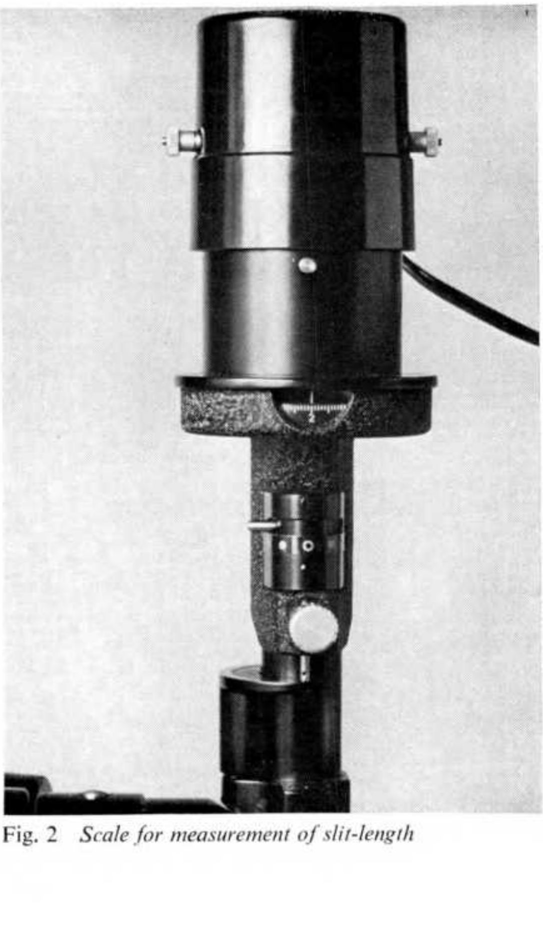

Fig. 2 *Scale for measurement of slit-length*

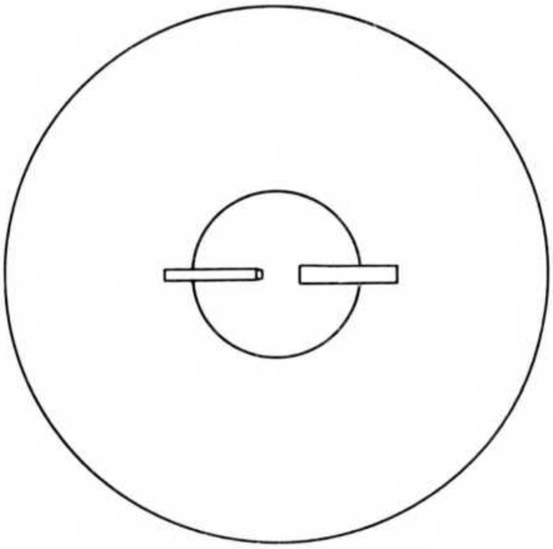

Fig. 3 *Horizontal slit beam in position A*

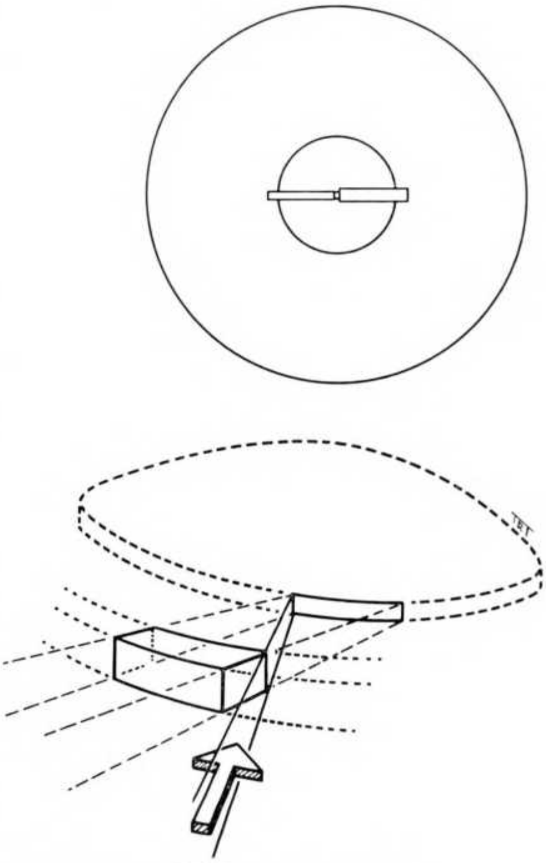

Fig. 4 *Horizontal slit beam in position B*

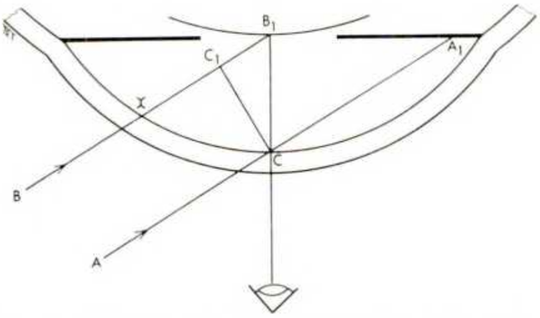

Fig. 5 *Simplified optical diagram of slit beam traversing the anterior chamber*

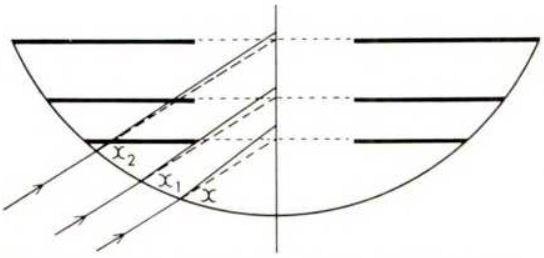

Fig. 6 *The path of the left-hand edge of the slit beam to show deviation at its point of incidence at the cornea. The wider the slit the less the deviation, since the incident angle decreases, as at* x, x₁, x₂ . . .

Therefore the length of CB_1 (the depth of the anterior chamber) is as follows:

$$\text{Sin } 60^\circ = \frac{CC_1}{CB_1} \qquad \text{or} \qquad CB_1 = \frac{CC_1}{\text{Sin } 60^\circ}$$

Now sin 60° is 0·866. Thus, with a slit length of, say, 2 mm, the anterior chamber depth should be

$$\frac{2}{0{\cdot}866} = 2{\cdot}309.$$

But this would be true only if no refraction of the beam occurred, which is obviously not the case. In fact the deviation of the left-hand edge of the beam is what is of significance in the observation which has to be made (Fig. 6), and this affects both the length of side CC_1 and angle C_1B_1C in Fig. 5.

Furthermore, referring again to Fig. 6: as the slit is lengthened the deviation of its left-hand edge at points x, x_1, x_2, etc., becomes progressively less, further complicating any attempt at an accurate computation of chamber depth.

Fig. 7, which is taken from Jaeger's paper, shows the optical conditions for a ray entering the eye. Ignoring most of the labelling, which is used in Jaeger's text to develop a slightly different theme, we find the ray of interest in our case is ray number 2 (entering at 40° instead of 60°, as in our method). The diagram shows clearly how the ray is deviated towards the normal to the cornea OA, thus changing the position of the anterior lens surface from its true position *C* to an apparent position *B*.

Since the present method did not appear to be suitable for deriving the chamber depth by direct calculation, it was decided to proceed by making a series of observations and comparing the slit length required to attain position *B* (Fig. 4) with an anterior chamber-depth measurement by means of the conventional attachment to the Haag-Streit slit lamp.

The results are shown in Table 1 and Fig. 8. It will be seen that there is a very good correlation between the 2 sets of readings.

The ratio of the means of:

$$\frac{\text{Goldmann readings}}{\text{Slit lengths}} = 1{\cdot}395.$$

If there were to be a simple proportional relationship between the two, then multiplying the slit length by 1·395 (say, 1·4) should give the Goldmann equivalent. Testing this method on a number of occasions subsequently has shown that this is broadly true, but again there appears to be some inconsistency in results which remains to be explained.

Analysis of the figures can be carried out by comparing each Goldmann result with its corresponding 'slit-length' reading to see how consistent the results are. The regression coefficient of Goldmann readings against slit-length readings can be calculated in two ways—either taking the Goldmann readings as the independent variable and the slit-length as the dependent or *vice versa*. In the first instance, having determined the regression

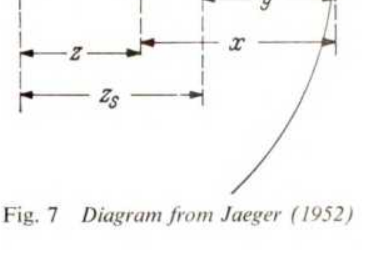

Fig. 7 *Diagram from Jaeger (1952)*

Table 1 *Slit readings. Numbers 3, 13, 21 isolated right eyes; numbers 42, 50, 56 isolated left eyes; in the remainder right and left pairs are present but are not arranged as pairs in the Table*

Eye No.	*Slit length* (*x value*)	*Actual Goldmann readings* (*y value*)	*Calculated Goldmann readings* (*y predicted*)	*Error*
1	1·5500	2·1000	2·2394	+0·1394
2	1·9500	2·6000	2·6862	+0·0862
3 R	2·4000	3·2000	3·1889	−0·0111
4	1·7000	2·5000	2·4070	−0·0930
5	2·3000	3·0500	3·0772	+0·0272
6	1·5000	2·2000	2·1835	−0·0165
7	1·5500	2·5000	2·2394	−0·2606
8	1·8000	2·4000	2·5187	+0·1197
9	1·6000	2·2000	2·2953	+0·0953
10	1·4000	1·9000	2·0718	+0·1718
11	2·1000	2·9000	2·8538	−0·0462
12	2·1000	2·8000	2·8538	+0·0538
13 R	3·1000	3·7000	3·9709	+0·2709
14	1·6000	2·1000	2·2953	+0·1953
15	2·2500	3·0500	3·0214	−0·0286
16	2·0000	2·8000	2·7421	−0·0579
17	1·6500	2·7500	2·3511	−0·3989
18	2·1000	2·8000	2·8538	+0·0538
19	2·0000	2·7500	2·7421	−0·0079
20	1·1000	1·7000	1·7367	+0·0367
21 R	1·2000	1·7000	1·3484	+0·1484
22	1·7300	2·3300	2·4405	+0·1105
23	1·2500	1·9000	1·9043	+0·0043
24	1·6000	2·3500	2·2953	−0·0547
25	2·2000	3·1500	2·9655	−0·1845
26	1·4000	2·0000	2·0718	+0·0718
27	2·0000	2·9000	2·7421	−0·1579
28	2·0500	2·7000	2·7978	+0·0979
29	1·5500	2·2000	2·2394	+0·0394
30	1·9500	2·7500	2·6862	−0·0638
31	1·8000	2·5500	2·5187	−0·0313
32	2·3000	3·0500	3·0772	+0·0272
33	1·5000	2·2000	2·1835	−0·0165
34	1·7000	2·6000	2·4070	−0·1930
35	1·7500	2·4500	2·4628	+0·0128
36	1·4000	2·1500	2·0718	−0·0792
37	1·3500	1·9500	2·0160	+0·0660
38	2·2000	2·9000	2·9655	+0·0655
39	2·1000	2·8000	2·8538	+0·0538
40	1·6000	2·3000	2·2953	−0·0047
41	2·3000	3·1500	3·0772	−0·0728
42 L	1·6000	2·3000	2·2953	−0·0047
43	2·1000	2·8000	2·8538	+0·0538
44	1·6000	2·2500	2·2953	+0·0453
45	2·1300	2·9000	2·8873	−0·0127
46	2·1000	2·7500	2·8538	+0·1038
47	1·4000	1·9000	2·0718	+0·1718
48	1·7300	2·5000	2·4405	−0·0595
49	1·2500	1·9500	1·9043	−0·0457
50 L	2·6000	3·4800	3·4123	−0·0677
51	1·6000	2·4000	2·2953	−0·1047
52	2·3000	3·1500	3·0772	−0·0728
53	1·9500	2·7000	2·6362	−0·0138
54	2·0000	3·0000	2·7421	−0·2579
55	2·0500	2·7500	2·7979	+0·0479
56 L	1·2000	1·8000	1·8484	+0·0484

Standard deviation of the errors = ±0·1176

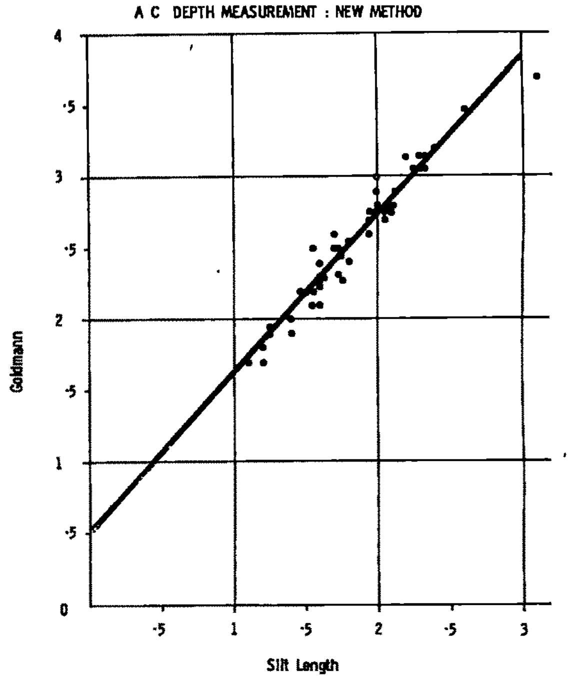

Fig. 8 *Plot of slit length readings against corresponding Goldmann observations (left and right eyes).*

Slope (m) = 1·117. SE = 0·04068. Intercept on y axis = 0·5079. Correlation coefficient = 0·96603. x mean = 1·82661. y mean = 2·54839

coefficient and intercept on the *y* axis, the expected slit-length reading corresponding to the actual Goldmann reading can be calculated, and in each case there is found to be a small error (known as the residual). A preliminary study of this (not illustrated) suggested an error of approximately 0·100.

One is now in a position to look at the regression using the slit-length readings as though they were the independent variables and thus calculating what the Goldmann reading ought to be if the slit reading was in fact 'correct'. (This is rather like having a thermometer marked with a scale in some sort of arbitrary units: after a suitable series of experiments one is able to say that a given reading on the arbitrary scale corresponds to a certain reading on a thermometer accurately marked in degrees Celsius; although in our case the arbitrarily marked thermometer, our slit reading, *and* the so-called accurate thermometer, the Goldmann readings, are probably both subject to some errors.) Clearly, however, the method is of no use if one has to refer each slit reading to the computer centre, so that a simple method of converting slit-length readings to anterior chamber depth is required. This can be done most easily by referring to a graph setting out the regression line of slit length against Goldmann readings or by calculation using this formula:

$y = mx + b$ where m is the slope (regression coefficient) and b is the intercept on the y axis.

Substituting these figures we have:

Calculated Goldmann reading = (1·117 × slit reading + 0·5079).

Using no. 1 in the Table as an example, we find that the slit length found (1·5500) gives a calculated Goldmann reading of 2·2394, whereas the Goldmann reading actually found was 2·100, an error of 0·1394. Similarly, in no. 19, where the slit-length reading is 2·0000, the Goldmann reading can be calculated as 2·7421, whereas the reading actually found was 2·7500, an error of –0·0079.

In short, therefore, it appears that the slit-length method consists in measuring the slit length required for coincidence as described, multiplying the result by 1·117, and adding 0·5079, or, simplifying, G = SL × 1·1 + 0·5, an extremely simple and quick calculation.

The error to be expected in such a method can be approximately determined by calculating the standard deviation of the errors listed in the right-hand column in the Table. This comes out at ±0·1176.

There remains, however, the anomaly that as slit-length and Goldmann readings approach zero they should, theoretically, reach it at the same time. In other words the regression line in Fig. 8 ought to pass through zero, which it does not.

In fact the relationship between slit-length and chamber depth is probably not properly represented by a straight line owing to the influence of the corneal refraction varying at different slit lengths, as shown on Fig. 6. Dr Swinscow (personal communication) feels that it is possible to envisage a shallow curve passing through most of the points which would unite a position near 0 with the outermost dot in the right-hand corner, but that a straight line provides a good approximation within a range that excludes the top right-hand dot.

The final conclusion, therefore, has to be that an exact and simple relationship cannot be demonstrated over the whole range, but for slit lengths of 1 to 2·5 mm the simple ratio quoted earlier (1·4) is sufficiently near the truth to be of clinical utility. In practice this is of great clinical value for the following reasons. Slit lengths of below 1 mm cannot be used because they are not marked on the instrument, and slit lengths in excess of 2·5 mm imply a chamber depth of at least 3·0 mm, as shown on the graph.

In summary, it seems reasonable to claim that the technique provides a quick method of estimating chamber depths between the range of 1·4 and 3·0 mm, a useful range in many clinical conditions.

Discussion

A quick and simple method of measuring anterior chamber depth is especially useful in closed-angle glaucoma, where the diagnosis may depend to some degree on recognition of a shallow chamber and the ability to measure it.

Although mydriatic glaucoma is rare, it is helpful to have a record of the chamber depth before instillation of a mydriatic, particularly, when a clinical estimate by simple observation has given rise to suspicion. A chamber depth of 2 mm or less should be regarded with considerable anxiety, especially if mydriasis is contemplated.

Variations in chamber depth at various times, for example, before and after mydriatics or miotics, are sometimes of interest and may be surprisingly large. Similarly, variations in depth between the 2 eyes may also be found, especially where there are unequal degrees of maturity of cataract. An eye with a mature cataractous lens may show either a much shallower or, alternatively, a much deeper chamber than the fellow eye, since the lens may swell or shrink when cataractous.

Measurement of anterior chamber depth is also valuable before considering implantation of an acrylic lens in the anterior chamber.

A final point may be of some interest: the coincidence method of measuring chamber depth measurement tends to give very similar values for the right and left eye, and it will be noted that the technique is symmetrical, the incident beam being directed in each eye from the temporal side and the axis of observation being approximately along the optic axis. In the Haag-Streit depth-measuring apparatus the incident beam enters along the optical axis, but the observation axis is not symmetrical for the 2 eyes, being from the nasal side in the case of the right eye and the temporal for the left.

I have detected a slight, but definite tendency for the anterior chamber depth estimate on the left eye by the Haag-Streit method to be slightly higher (by 0·023 mm). This has also been reported by Lowe (1968). It seems unlikely that the left chamber is in fact deeper than the right, and the coincidence method described does not indicate that this is so, since by this method the difference is 0·003. Hence it may be that this new method of measuring chamber depth is in fact slightly more accurate than the Goldmann system in some respects, not of course in providing an actual measurement of depth, which it is unable to do, but in so far as it can confirm that 2 chambers are of exactly equal depth.

My thanks are due to the Statistical Department at the Institute of Ophthalmology, and to Dr T. D. V. Swinscow for valuable advice and to Miss J. Quaife for secretarial assistance.

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One gonioscopic fallacy

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SUMMARY Traditional gonioscopic practice assumes that, if most of the angle is gonioscopically closed, intraocular pressure increases. Evidence is produced to show that this is fallacious, because at its inception angle closure is iridocorneal contact occurring on the corneal side of the limbus. Although the angle cannot be seen by means of a gonioscope, there is initially no iridotrabecular contact. It is only after pressure increases that iris is pushed against trabecular meshwork and the angle is truly closed.

It is generally accepted by gonioscopists that when 70% of the angle is gonioscopically closed intraocular pressure increases (Becker and Shaffer, 1961; Duke-Elder and Jay, 1969). The purpose of this paper is to show that, and explain why, this is fallacious.

Case history

A woman aged 76 presented with acute closed-angle glaucoma in the right eye. The result of a provocative test in the untreated left eye is recorded in Fig. 1. At zero hour intraocular pressure was 15 mmHg, facility of outflow 0·40 μl/mmHg per min, pupil diameter 3·3 mm, and gonioscopy revealed an open narrow angle (grade II). Pilocarpine 2% and phenylephrine 10% drops were instilled. One hour later intraocular pressure was 14 mmHg, facility of outflow 0·49, pupil diameter 2·9 mm, and gonioscopy showed the angle to be closed in 30% of its extent. At this point more pilocarpine and phenylephrine drops were instilled. After the lapse of another hour (that is 2 hours from the start of the test) intraocular pressure was 14 mmHg, outflow 0·49, pupil diameter 3·3 mm, and the angle was gonioscopically closed in 80% of its extent. Another drop of phenylephrine was instilled, but thereafter no more drugs were given. Pressure, outflow, and pupil diameter were again measured at 3 and 4 hours from the start, with no significant change in any of these. In addition gonioscopy showed that at least 70% of the angle remained gonioscopically closed.

Discussion

In this patient, therefore, substantial gonioscopic closure of the angle occurred yet there was no increase in pressure, nor did outflow decrease. It is emphasised that this is not a unique case, approximately 30% of eyes at risk of developing closed-angle glaucoma (because the fellow eye has had a spontaneous acute attack) do not produce

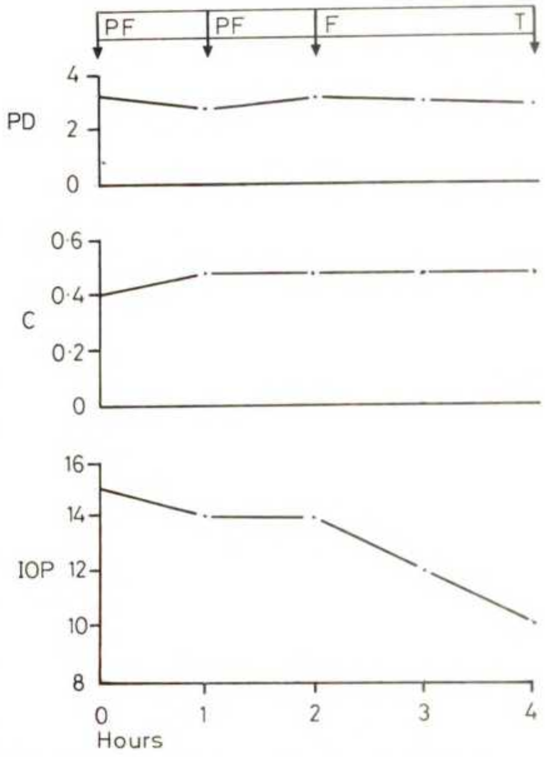

Fig. 1 *Provocative test result in an eye at risk of closed-angle glaucoma. In spite of substantial gonioscopic angle closure, pressure and outflow did not change significantly*

P = pilocarpine. T = thymoxamine. F = phenylephrine

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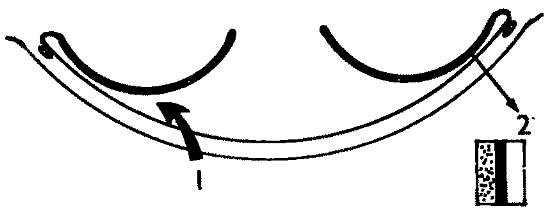

Fig. 2 *Diagram of an anterior segment with iris bowing forwards towards cornea. Angle narrowness and the presence or absence of closure can be diagnosed either with a gonioscope (position 1) or by noting the distance between iris and cornea internal to the limbus (position 2)*

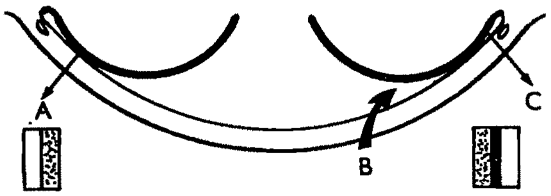

Fig. 3 *At its inception angle closure is really iridocorneal contact along a strip on the corneal side of the limbus. Viewed from* A *(with a slit beam) the angle is closed. From* B *(with a gonioscope) too the angle cannot be seen and is judged to be closed. However, because of the differing curvatures of iris and cornea and the shape of the angle recess the angle is not truly closed. Moving the slit beam to* C *shows a gap between iris and cornea*

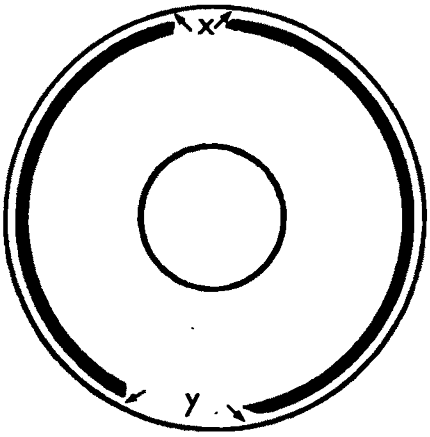

Fig. 4 *Because angle closure is initially iridocorneal contact, most of the angle may appear to be closed (gonioscopically), yet pressure may not increase nor outflow decrease. Aqueous can still gain access to all of the trabecular meshwork through the gaps at* x *and* y

a positive provocative test (that is, a pressure increase of at least 8 mmHg with gonioscopic closure). Yet of these 30% substantial gonioscopic closure of the angle does occur on provocative testing in most (70%) (Mapstone, 1977). It is therefore clear that much of the angle can close—gonioscopically—yet pressure does not increase nor outflow decrease. What is the explanation?

There are two possible reasons why pressure did not increase in this patient—either insufficient time elapsed after closure for a significant pressure rise to occur, or gonioscopic closure does not necessarily indicate true angle closure.

The first of these explanations is improbable, because 4 hours had elapsed before the test was

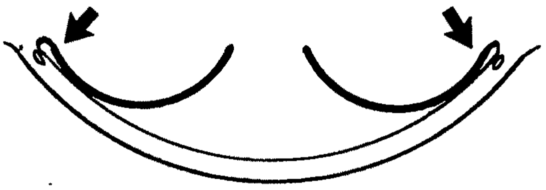

Fig. 5 *The angle becomes truly closed only when, as a result of iridocorneal contact, pressure increases. Peripheral iris is now actively pushed on to trabecular meshwork*

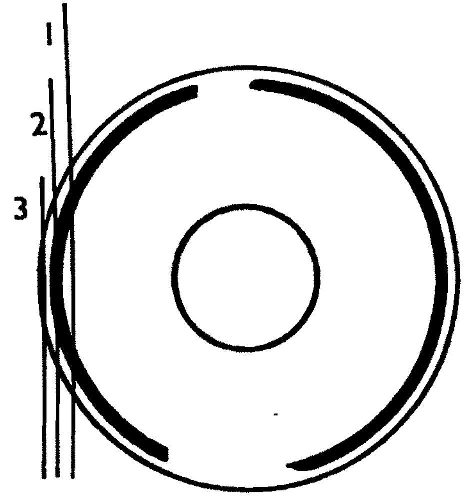

Fig. 6 *Because of the mechanism of initial angle closure a slit beam shone in at 3 will show an open angle. At 2 there is iridocorneal contact throughout most of its length but not at the extremities. However, a beam at 1 will show iridocorneal contact at the extremities but not in the middle*

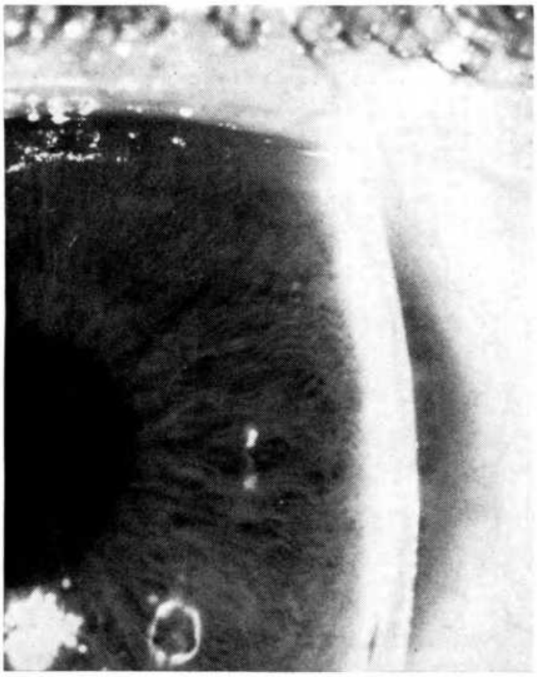

Fig. 7 *Photograph of an eye provoked to gonioscopic closure. There is iridocorneal contact throughout most of the length of the slit beam but not at its lower extremity. Note the position of the slit relative to the limbus*

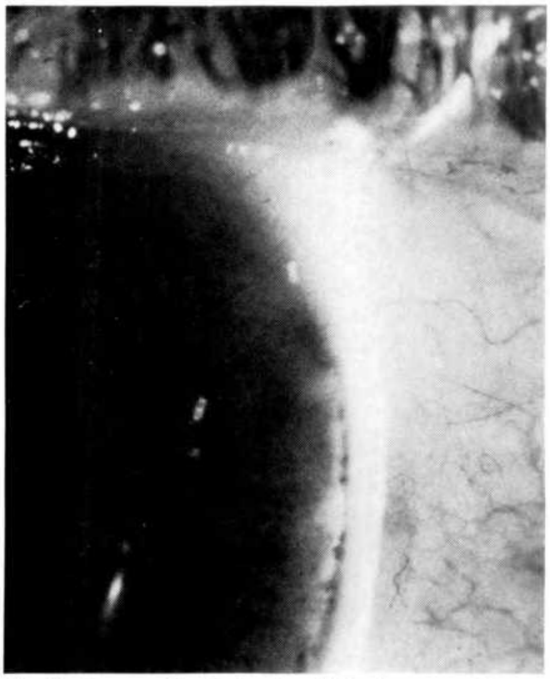

Fig. 8 *Same as Fig. 7, but the slit has been moved nearer to the limbus. There is a clear gap between iris and cornea*

terminated. The second needs examining and implies that currently accepted inferences from gonioscopy are incorrect. The crucial question is, how do angles close? An intuitive analysis follows.

Fig. 2 represents in diagrammatic form an anterior segment with iris bowing forwards towards cornea. Angle narrowness can be assessed either with a gonioscope (position 1) or a slit beam may be shone in on the corneal side of the limbus and the distance between iris and cornea 'measured' in terms of corneal thickness (position 2). In the situation shown the angle is clearly open. Two other points are apparent from Fig. 2. Firstly, the angle is not really a geometric angle at all but a recess, since a finite distance exists between the insertion of iris root into ciliary body and the ciliary body/trabecular meshwork junction. Secondly, the curvature of the anterior iris surface is not the same as that of the cornea.

When, therefore, iris is sufficiently displaced to 'close' the angle (gonioscopically) the situation shown in Fig. 3 obtains. Viewed from position *A* (with a slit beam) there is iridocorneal contact and the angle is closed, from position *B* (with a gonioscope) the angle is also closed. But if the slit beam is moved more towards the limbus (position *C*) the angle is clearly open, that is, the inception of gonioscopic angle closure is really iridocorneal contact along a strip on the corneal side of the limbus.

If this is a correct interpretation, the situation shown in Fig. 4 will be one possible consequence. If 80% of the angle is gonioscopically closed, aqueous can still gain access to *all* of the trabecular meshwork through x and y, so that pressure may not increase nor outflow decrease. If the gap between iris and cornea at x and y is sufficiently narrow, pressure may increase and outflow decrease—but not necessarily enough to produce a 'positive' provocative test. If, however, pressure increases sufficiently, the situation shown in Fig. 5 obtains. An increased pressure now pushes peripheral iris against trabecular meshwork, and the angle becomes truly 'closed'. A vicious circle is generated, and the end result is a positive provocative test or acute closed-angle glaucoma.

The validity of this explanation can be readily demonstrated. Fig. 6 shows that, in an eye provoked to 80% angle closure (but without a pressure increase), if a slit beam is shone in at line 2 there is iridocorneal contact throughout most of its extent, but not at the two extremities. If, however,

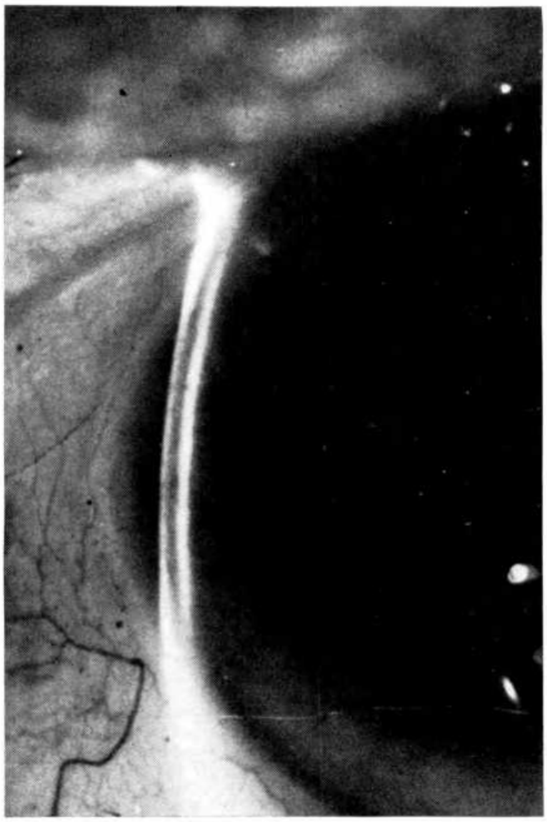

Fig. 9 *Photograph of an eye, provoked to gonioscopic closure. There is iridocorneal contact throughout the length of the slit beam*

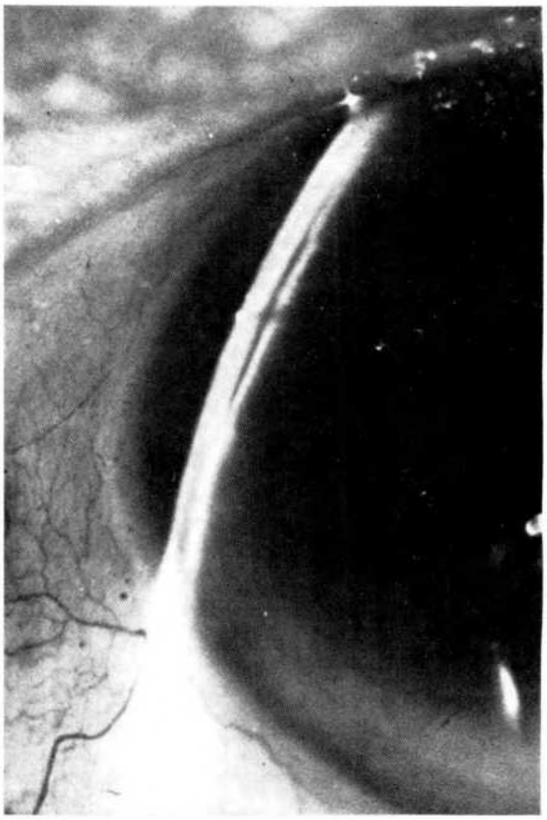

Fig. 10 *Same as Fig. 9. The slit has been tilted towards the corneal axis. A gap appears between iris and cornea at the middle of the beam (see line 1, Fig. 6)*

the slit beam is moved to position 3, the angle is open. Fig. 7 shows an eye provoked to gonioscopic closure (with pilocarpine and phenylephrine). There is iridocorneal contact—except inferiorly—and this has occurred well to the corneal side of the limbus. If the slit beam is now moved nearer to the limbus (Fig. 8), the angle is clearly open.

Fig. 6 also shows that if the slit beam is moved from position 2 (closed) to position 1 there will be iridocorneal contact at the extremities of the beam only. Figs 9 and 10 demonstrate this in a patient.

More than 500 eyes have been provoked to partial or complete angle closure with pilocarpine and phenylephrine, and the mechanism has always been as described above. It is apparent, therefore, that gonioscopic closure does not necessarily imply true angle closure.

I thank Mrs E. Tubb for secretarial assistance.

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Diurnal changes of the intraocular pressure of patients with angle-closure glaucoma

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SUMMARY The diurnal curves of 21 patients (40 eyes) with angle-closure glaucoma and of 21 normotensive subjects (42 eyes) were studied. The patients with angle-closure glaucoma had a V-shaped diurnal curve that was completely different from the diurnal curve of the normotensive subjects. Most of the eyes of the patients with angle-closure glaucoma had a diurnal change of the intraocular pressure of 8 mmHg or more, while in the normotensive subjects only 1 eye had a diurnal change as large as 8 mmHg.

The average normal intraocular pressure (IOP) of healthy eyes has been extensively studied. Measurements taken with the Schiotz tonometer yielded an average IOP of 15·5 mmHg (Leydhecker *et al.*, 1958) to 17·0 mmHg (Weekers *et al.*, 1955) and with a Goldmann applanation an average of 14·5 mmHg (Draeger, 1959) to 15·6 mmHg (Levene, 1961). In the normal eye the IOP shows diurnal variations. The amplitude of the diurnal variations has been found to be 3 to 7 mmHg (Dobree, 1953; Alimuddin, 1956; Ericson, 1958; Katavisto, 1964; Duke-Elder and Jay, 1969), but in less than 1% of cases it was found to be as large as 10 mmHg (Drance, 1960). In about 40% of normal persons the IOP is somewhat higher in the early morning, while in about 60% it may reach its peak at random times during the day (Alimuddin, 1956; Drance, 1960; Katavisto, 1964; Daubs, 1973).

There is no available study of the diurnal curve of patients known or suspected to be suffering from angle-closure glaucoma (ACG). The present study deals with the diurnal curve of 21 patients (40 eyes) suffering from ACG and the diurnal curve of 11 (20 eyes) of these 21 patients 3 months after peripheral iridectomy.

Patients and methods

Twenty-one patients (40 eyes) aged between 38 and 65 years were referred to Hadassah University Hospital Eye Department with the diagnosis of angle-closure glaucoma. Subjective complaints were ocular pain in 16 patients, blurred vision in 7 patients, light haloes in 4 patients. The diagnosis of ACG was confirmed by the presence of some or all of the following findings: narrow angle gonioscopically during a normotensive period, a positive dark room test, and the closure of the angle while the IOP was raised.

Each patient was admitted to hospital and his IOP was measured 7 times a day at 3-hour intervals between 0600 h and midnight with the Goldmann applanation tonometer. The pressure measurements were carried out during 2 successive days.

After the diagnosis of ACG was confirmed a peripheral iridectomy operation was recommended to all patients, but only 11 (20 eyes) out of 21 patients agreed to be operated upon. Three months after the operation these 11 patients underwent repeated diurnal curve examinations as described above.

A control group of 21 normotensive persons (42 eyes) with normal looking angles, aged between 39 and 65 years, underwent the same diurnal curve examinations. They were admitted to hospital in the Eye Department because of ptosis (4 cases), dacryostenosis (11 cases), and immature cataract (6 patients). None of the patients or members of the normotensive control group, had either anterior or posterior synechiae or any other ocular lesions that would to our knowledge have a definite influence on the IOP.

All topical and systemic medications were stopped at least 48 hours before the examinations. IOP measurements were evaluated by the Mann-Whitney U test when appropriate.

Results

The mean and standard deviation of the IOP during each of the time points in the diurnal curve of the

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Table 1 *Mean and standard deviation of IOP in mmHg of the patients with ACG, the patients who had peripheral iridectomy, and the normotensive control group*

			Hours of measurement of IOP						
			0600 h	*0900 h*	*1200 h*	*1500 h*	*1800 h*	*2100 h*	*2400 h*
Patients with ACG		Mean	18·56	18·22	17·39	16·87	17·27	17·71	18·77
		SD	7·00	7·87	7·74	5·55	7·29	10·41	10·91
Patients who had peripheral iridectomy procedure	Before the operation	Mean	17·46	17·89	16·27	17·05	18·03	18·43	19·05
		SD	4·85	6·54	4·19	5·31	7·42	11·66	12·94
	After the operation	Mean	15·58	14·11	14·03	13·95	14·50	14·08	14·53
		SD	4·23	4·14	3·11	2·77	3·78	3·28	3·36
Normotensive control group		Mean	14·44	14·21	13·64	14·31	13·95	13·51	13·57
		SD	3·22	2·35	3·10	3·13	3·01	2·88	3·07

patients with ACG, the patients who underwent peripheral iridectomy, and the normotensive control group are given in Table 1 and Fig 1. It is seen that the patients with ACG had a higher IOP average than the normotensive control group. The highest IOP in the patients with ACG was at midnight, and at 0600 h the IOP was only slightly lower than that at midnight. The lowest IOP was at 1500 h. The curve had a V-shape with a statistically significant difference between the pressures at 0600 h and midnight and the pressure at 1500 h ($\mathrm{P}<0{\cdot}01$). In the normotensive control group the highest IOP was at 0600 h with a statistically insignificant change during the day ($\mathrm{P}>0{\cdot}05$). A statistical analysis proved that the diurnal curve of the patients with ACG was completely different from the diurnal curve of the normotensive control group ($\mathrm{P}<0{\cdot}01$). The patients who underwent a peripheral iridectomy showed a diurnal curve that was statistically similar to that of the normotensive control group ($\mathrm{P}<0{\cdot}05$).

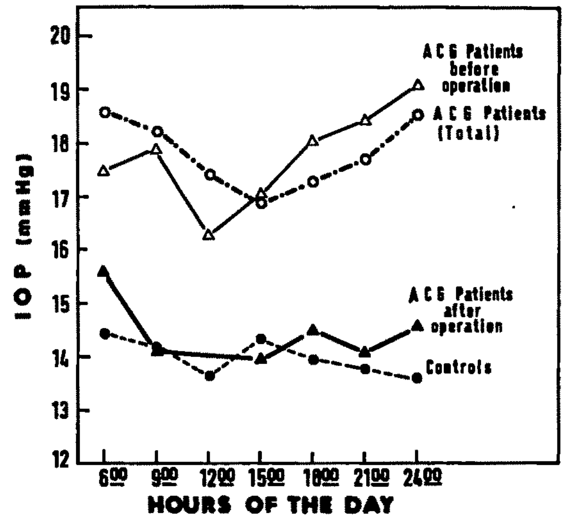

Fig. 1 *Diurnal curve of IOP of the patients with ACG, the patients with ACG who had peripheral iridectomy before and after the operation, and the normotensive control group*

The diurnal changes in the patients with ACG, the patients after undergoing peripheral iridectomy, and the normotensive control group are given in Fig. 2. A diurnal change of 8 mmHg was noted in the control group in 1 eye, and only in 1 of the 2 diurnal curve examinations performed on that eye. In the patients with ACG a diurnal change of 8 mmHg or more, at least in 1 of the 2 diurnal curve examinations, was noted in 26 (65%) eyes. In the patients who underwent peripheral iridectomy the diurnal changes in IOP were not as great as before the operation, but still 8 eyes (40%) had in 1 of the 2 diurnal curve examinations a change of 8 mmHg or more. The largest diurnal variation in the patients with peripheral iridectomy was 12 mmHg.

In each of the diurnal curve examinations the lowest IOP measurements of the patients with ACG ranged between 7 and 25 mmHg, with mean of 13·7 mmHg and a median of 20·0 mmHg. The lowest IOP measurements of the normotensive control group ranged between 7 and 16 mmHg, with a mean of 11·5 mmHg and a median of 12·0 mmHg.

Discussion

The present study includes a comparison of the diurnal curve and the diurnal change of patients with ACG and a normotensive control group. The difference between the diurnal curves is highly significant ($\mathrm{P}<0{\cdot}01$). In the patients with ACG the

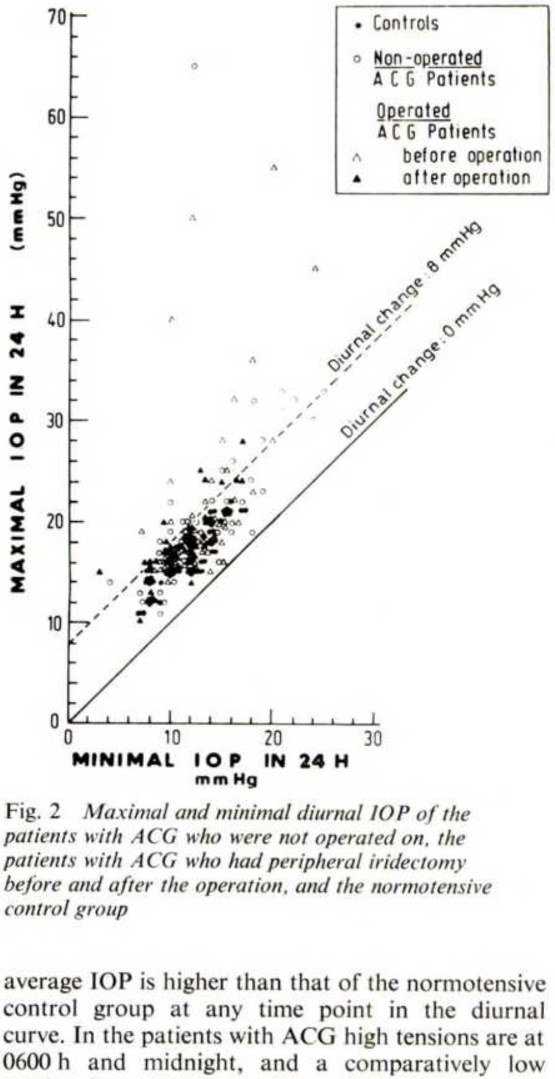

Fig. 2 *Maximal and minimal diurnal IOP of the patients with ACG who were not operated on, the patients with ACG who had peripheral iridectomy before and after the operation, and the normotensive control group*

average IOP is higher than that of the normotensive control group at any time point in the diurnal curve. In the patients with ACG high tensions are at 0600 h and midnight, and a comparatively low tension is at 1500 h, giving to the diurnal curve a V-shape. The diurnal curve in the normotensive control group has no significant fluctuations. Dilatation of the pupil in darkness with subsequent disturbance to the aqueous drainage can explain the V-shape of ACG patients' diurnal curve. Patients after peripheral iridectomy have a diurnal curve that is more like that of the control group, and that is due to the abolition of the possibility of a pupillary block.

In other studies (Dobree, 1953; Alimuddin, 1956; Ericson, 1958; Katavisto, 1964), as well as in our control group, the IOP variations of the normal people rarely exceeded 8 mmHg. Therefore we adopted Drance's definition that a diurnal variation of 8 mmHg or more is abnormal (Drance, 1960). A change of 8 mmHg or more was noted at least in 1 of the 2 days' diurnal curves in 65% of the eyes of the patients with ACG, while in the normotensive control group there was a change of 8 mmHg in 2% of the eyes, and the rest had a lower diurnal change. We have no explanation of the finding that in 40% of the eyes of the patients after peripheral iridectomy there was still a change of 8 to 12 mmHg, at least in 1 of the 2 days' diurnal curves. That change was in spite of the fact that none of the patients had plateau iris.

It is worth noting that most of the patients with ACG have IOP measurements during some hours of the day which are almost as low as those of the normotensive control group. These patients are usually given a provocative test to detect increase of IOP. It seems to us that provocative tests are influenced by the pressure at the beginning of the test and by the trend of the diurnal curve. A patient suspected of having ACG may on one occasion have a positive result and on another a negative result merely because the examinations are started at 2 different points of the diurnal IOP curve. We intend to investigate that carefully.

The present study shows that a diurnal curve with a V-shape and a difference of 8 mmHg or more during 24 hours can be a valuable test confirming the diagnosis of ACG. Its results are not subject to artifacts as those of the provocative tests may be.

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Comparison of the pupillary, refractive, and hypotensive effects of Ocusert-40 and pilocarpine eyedrops in the treatment of chronic simple glaucoma

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SUMMARY Twelve patients with chronic simple glaucoma were treated for 1 week with Ocusert-40, and the effects on the pupil, intraocular pressure, and refraction were measured. A comparison was made with the effects of pilocarpine eyedrop therapy in 8 of these patients. Both forms of pilocarpine treatment gave satisfactory control of intraocular pressure and both constricted the pupil to a similar degree shortly after initiation of treatment. During the week on Ocusert-40 the pupils redilated, so that 54% of the initial miosis remained after 7 days' wear. There was, however, considerable variability in the pupillary sensitivity to Ocusert-40 within and between eyes, and it is suggested that this may have been partly due to variable release rates of pilocarpine. Only minor decreases in visual acuity and refraction resulted from pilocarpine in either form. Seven of the 12 patients rejected Ocusert-40 because of discomfort or inability to retain the device.

Pilocarpine eyedrops have been widely prescribed for glaucoma for many years despite two major disadvantages. Firstly, they need to be instilled 3 or 4 times daily, which encourages non-compliance (Vincent, 1971), with the consequent risk of inadequate pressure control. Secondly, the drops deliver a large dose which initially causes side effects of browache, darkening of vision due to pupillary constriction, and myopia. Ocuserts appear to offer a promising alternative to conventional drop therapy because their continuous release of lower drug concentrations has been reported to cause relatively few side effects while adequately controlling pressure (Brown *et al.*, 1976; Drance *et al.*, 1977; Hillman *et al.*, 1977). This study was designed to confirm these reports by comparing the pupillary, refractive, and ocular hypotensive effects of Ocusert-40 with conventional drop therapy in a group of glaucoma patients.

Patients and methods

PATIENTS

Twelve patients with bilateral chronic simple glaucoma volunteered for the study. Four of them were recently diagnosed and untreated cases and 8 had been treated previously with pilocarpine eyedrops only, for periods that varied from 1 week to 6 years. Details of the patients and their treatments are given in Table 1. All oral treatments for other diseases remained unchanged throughout the period of study.

TREATMENTS

The investigation had a total duration of 15 days (Fig. 1). Only patients 1–8, previously treated with pilocarpine eyedrops, completed the whole study; the remaining 4 patients entered at day 8. On day 1 the patients were given their final application of drops and the effects were noted. Pilocarpine treatment was then stopped and dummy Ocuserts were inserted to familiarise the patient with this type of treatment. The patient was unaware that the Ocuserts were drug-free. The dummies were worn for 1 week, during which time no pilocarpine was given, but treatment was continued with oral acetazolamide (Diamox Sustets 500 mg twice daily). On day 8 the acetazolamide was stopped and the dummy Ocuserts were replaced by Ocusert-40 systems (May & Baker Ltd.), which in the steady state release pilocarpine at a rate of 40 µg/h. These were also worn for 1 week, after which the patients were given the choice of drops or Ocuserts for continuation of therapy.

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Table 1 *Details of patients*

				Previous pilocarpine eyedrop treatment		
No.	*Age*	*Sex*	*Race*	*Concentration (%)*	*Duration*	*Other drug treatments (oral administration)*
1	68	Male	Caucasian	4	2 weeks	Propranolol 20 mg 3 times a day Glyceryl trinitrate as required
2	70	Female	Asian	4	2 weeks	—
3	54	Male	Caucasian	1	6 years	—
4	56	Male	Caucasian	2	18 months	Propranolol 40 mg 3 times a day
5	62	Female	Caucasian	4	1 week	—
6	67	Male	Caucasian	2	9 months	—
7	51	Female	Negro	4	1 week	Timolol 10 mg 4 times a day Methyldopa 500 mg 3 times a day
8	65	Male	Caucasian	2	2 weeks	Acebutolol 100 mg 4 times a day Prazosin 2 mg 3 times a day Chlorpropamide 100 mg once daily
9	47	Female	Caucasian	—	—	Acetazolamide (Sustet) 500 mg twice daily (stopped during study)
10	49	Male	Caucasian	—	—	—
11	76	Female	Caucasian	—	—	Cyclopenthiazide 0·5 mg once daily Diazepam 2 mg once daily
12	56	Female	Caucasian	—	—	—

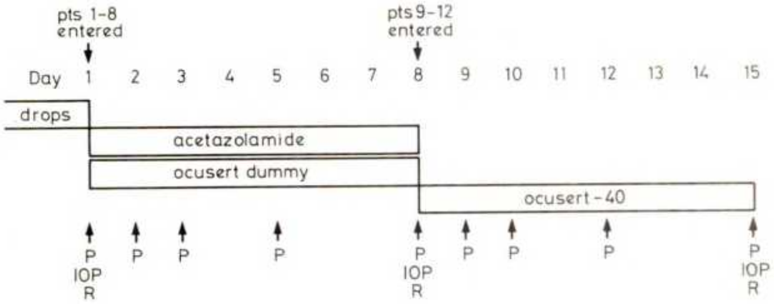

Fig. 1 *Design of experiment showing when pupil (P), intraocular pressure (IOP), and refraction (R) meaurements were performed*

Most patients preferred to wear the Ocuserts in the upper fornix.

MEASUREMENTS

The intraocular pressure (IOP), resting pupil diameter, visual acuity, and refraction were measured for both eyes on the days indicated. IOP was measured by applanation tonometry under local anaesthesia with benoxinate 0·4%. Three readings were recorded from each eye, the tonometer dial being read and reset by an independent observer. Resting pupil diameters were recorded in darkness with a Whittaker Series 1800 infrared television pupillometer (Smith *et al.*, 1978). Visual acuity was measured at 5 m with a 5-m Snellen chart. Changes induced by pilocarpine were related to baseline values for visual acuity and refraction, which for patients 1 to 8 were the readings taken 5 to 6 hours after their last drops on day 1 and for patients 9 to 12 were those taken before Ocusert treatment on day 8. Refraction was found objectively by retinoscopy when possible and subjectively by the use of a duochrome Snellen chart.

Results

INTRAOCULAR PRESSURE

The IOP (mean ± standard error) in the 16 eyes from 8 patients previously treated with drops was 21·3±0·7, 18·5±0·9, and 21·2±0·6 mmHg after eyedrops, acetazolamide, and Ocusert therapy respectively. Whereas all 3 treatments gave satisfactory control, the pressure after acetazolamide was significantly lower ($P < 0{\cdot}001$) than after either form of pilocarpine treatment. In the 4 patients who had not previously received eyedrops the mean IOP was 25·5±2·3 and 19·6±1·2 mmHg before and after Ocusert treatment respectively.

PUPIL RESPONSES

Recovery of the pupil diameter after cessation of eyedrop therapy was complete in 2 to 4 days. After insertion of Ocusert-40 the mean diameter fell from 5·23 to 1·93 mm at 1 hour. During the following week (Fig. 2) the pupils gradually recovered to a final mean size of 3·45 mm on day 15. Thus 54% of the maximum miotic effect of Ocusert-40 remained at the end of the week.

In patients 1 to 8 the peak effect of Ocusert-40 was compared with that resulting from 1 drop of pilocarpine at the concentration prescribed for each individual (see Table 1). No difference was found in the size of the pupil at the maximum effect of each treatment (1·70 mm after drops and 1·63 mm after Ocusert). In the Caucasian patients peak effects occurred at approximately 40 minutes after drops and 1 hour after Ocusert insertion, but in the Asian and Negro patients the time course of both pilocarpine treatments was delayed. Thus the peak effect of Ocusert in the 2 non-white patients was measured on day 9 at a time when the pupils of all the white patients were recovering.

There was considerable variability in the pupillary response to Ocusert-40, illustrated by the two extremes in Fig. 3. The left pupil of patient 10 had recovered completely by the end of the week, and this corresponded with a poor response of IOP. Pressures before and after Ocusert were 39 and 29 mmHg respectively compared with 47 and 14 mmHg respectively in the right eye which retained a pupillary effect. In contrast, the pupil of the right eye of patient 9, in which the pressure response was good, was still tightly constricted on day 15.

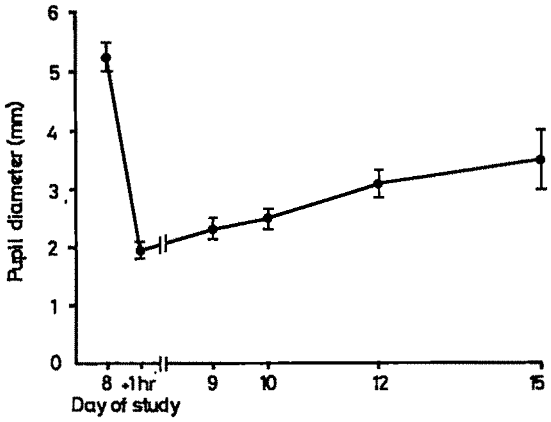

Fig. 2 *Pupil diameters in 12 patients treated with Ocusert-40. Data for day 8 show the diameter before and 1 hour after insertion. Three eyes were unsuitable for television pupillometry, hence the mean and standard errors shown are from 21 eyes*

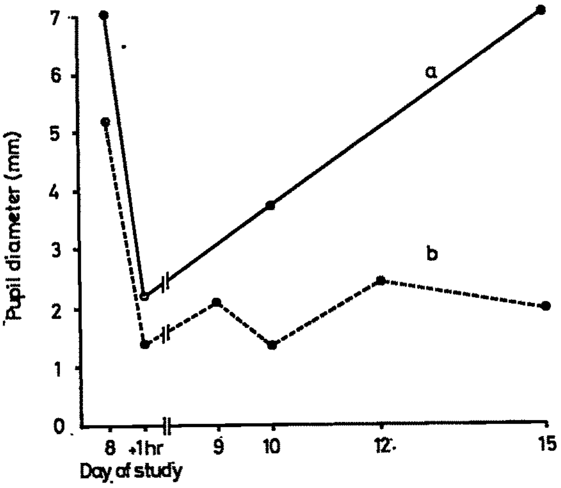

Fig. 3 *The pupil size in* (a) *patient 10, left eye; and* (b) *patient 9, right eye during Ocusert-40 treatment illustrates the variability in pupillary response*

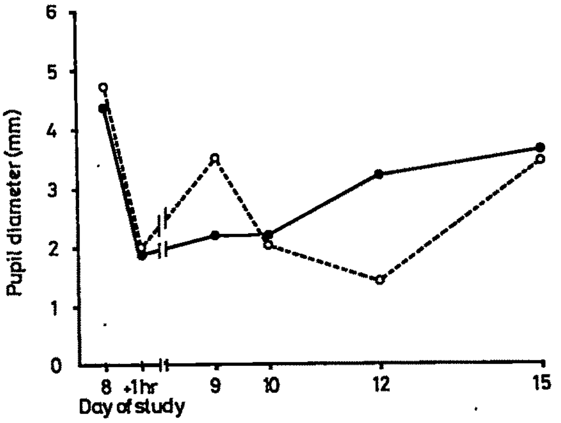

Fig. 4 *The pupillary response of the left* (●) *and right* (○) *eyes of patient 5 during Ocusert-40 treatment. On day 12 there was an intense miosis in the right eye, which was red and sore*

Fig. 4 illustrates a phenomenon encountered in 5 of the 12 patients during the week with Ocusert-40 treatment. On day 12 this patient complained of soreness in his right eye, which had conjunctival injection and a pupil that had reconstricted to a very small size (1·37 mm). Within the group these reconstrictions, which interrupted the gradual pupillary redilatation, were always accompanied by complaints of discomfort and occurred most frequently in the second half of the week. This phenomenon did not occur once in the 8 patients who wore dummy Ocuserts for 1 week.

VISUAL ACUITY AND REFRACTION

In all patients studied only small changes were induced by pilocarpine given in drops or Ocuserts with mean values not exceeding a 1-line decrease in Snellen visual acuity and a 0·5 D myopic shift in refraction. The only marked pilocarpine effect was in patient 3, whose myopia increased by 1·5 D during the first hour after both drops and Ocusert-40. By the end of the week on Ocusert-40 his refraction had returned to its baseline value.

PATIENT ACCEPTABILITY

Patients were followed-up 1 to 3 months after completion of the study to check on the type of therapy they preferred. It was found that only 5 of the 12 were still using Ocuserts, the remainder having reverted to drops. The reasons for the failures were invariably given as 'discomfort' or that the Ocuserts 'kept falling out'.

Discussion

In confirmation of previous reports it was found that IOP was adequately controlled by Ocusert-40 therapy. The mean level of pressure was identical after pilocarpine in either delivery form, but acetazolamide gave a significantly better response. However, all the patients disliked the tingling sensation in the skin that accompanied acetazolamide therapy.

It has been reported that Ocusert-40 treatment is relatively free of the pupillary and refractive side effects of pilocarpine eyedrops (Brown *et al.*, 1976). The results of this study, however, show that shortly after pilocarpine was given in either form the pupil constricted to a size that probably represented its physical minimum diameter. Although the peak effects were thus comparable, with Ocuserts the pupils redilated, so that only half the initial miosis remained at the end of the week. Thus despite the unexpected pupillary constrictions that interrupted the course of this redilatation in some patients (Fig. 4), in general patients avoided the repeated fluctuations that occur with drop therapy.

Reports that Ocuserts affect visual acuity and refraction less than drops (Hillman *et al.*, 1977; Drance *et al.*, 1977) are not supported by this study, since here only minor changes were induced by both forms of pilocarpine. This was probably because all our patients were aged over 40 years, and, as noted previously, pilocarpine-induced myopia is rare in the older age group (Hitchings and Smith, 1977). Claims that Ocuserts have marked visual benefits based on studies with young normal subjects (Place *et al.*, 1975) are therefore of limited relevance, since the majority of patients with simple glaucoma are elderly.

Five of the 12 patients that received Ocusert-40 treatment experienced the phenomenon illustrated in Fig. 4 in which the pupil reconstricted to its minimum size and the conjunctiva became red and uncomfortable. As this phenomenon did not occur with the drug-free Ocuserts, it was presumably caused by a sudden leakage of pilocarpine in excess of the 'controlled' release rate. Such phenomena have been observed before (Lee *et al.*, 1975), though less frequently than in this study, probably because our patients were examined more often (on 5 of 8 days of treatment). The release of pilocarpine from Ocusert-40 may therefore be less predictable than is claimed by the manufacturers. Variability in release rates of individual Ocusert-40 systems may also have contributed to the differences in pupillary sensitivity in this group of patients.

Only 5 of the 12 patients who entered the study chose to continue with Ocusert-40 treatment. Other workers have reported similar drop-out rates (Hitchings and Smith, 1977; Hillman *et al.*, 1977). Some of our patients reverted to drops because they found Ocuserts uncomfortable to wear, and some of the more elderly had difficulty in retaining them under lax eyelids.

It is concluded that some patients, particularly younger ones, may benefit from a reduction in side effects when pilocarpine is administered in the form of Ocusert-40. However, the possibility that the drug release rate may suddenly increase needs further investigation.

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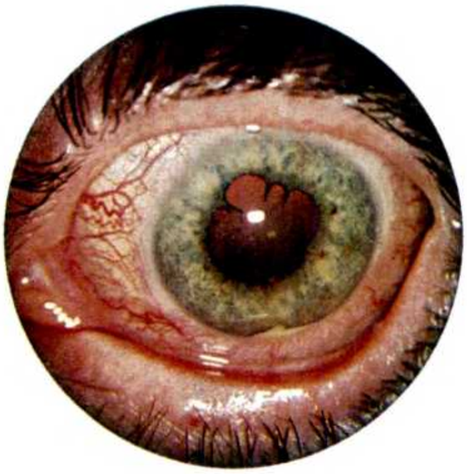

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British Journal of Ophthalmology, 1979, **63**, 233–235

Transient ocular hypertension following trabeculectomy

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SUMMARY A study of the postoperative evolution of 70 eyes subjected to trabeculectomy over a 3-year period is reported. This is the operation of choice in our department in cases of chronic open-angle glaucoma and chronic angle-closure glaucoma. The study showed that in 35·7% of the operated eyes the intraocular pressure was increased on the second postoperative day and became normal within a week. This raised intraocular pressure did not influence the final result of the operation.

Cairns (1968) was the first to introduce the trabeculectomy operation as a most successful form of surgery for primary open-angle glaucoma. The trabeculectomy operation causes a highly significant reduction of the intraocular pressure (IOP) and a parallel rise in aqueous outflow facility (Watson and Barnett, 1975).

Trabeculectomy is increasingly becoming the operation of choice in cases of primary open-angle glaucoma and chronic angle-closure glaucoma. For acute angle-closure glaucoma the usual procedure is still peripheral iridectomy, though it sometimes necessitates further treatment (Wilson, 1977).

Another group of eyes subjected to trabeculectomy are those treated by combined trabeculectomy and cataract extraction (Hilsdorf, 1974; Bregeat, 1975; Witmer and Rohen, 1976). Immediately after the operation, in 25 out of 70 eyes operated on by us the increase of the IOP was transient and had not affected the final result of the operation.

Materials and methods

The operation technique used is as described by Watson (1970), and re-described in a study by Thyer and Wilson (1972) with some minor modifications. The basic points of the operation are: (1) Creation of a conjunctival and Tenon flap placed 7 to 8 mm behind the limbus to keep it so far as possible from the scleral section. (2) Minimal cautery of sclera. (3) Creation of a lamellar scleral flap of 5/5 mm limbus based, one-third to one-half of the scleral thickness. (4) Excision of a 2/2 mm block of inner sclera from the corneoscleral limbus. (5) Peripheral iridectomy. (6) Closure of the scleral flap with 5 8–0 silk sutures. (7) Stitching of the conjunctiva with 6–0 continuous suture. (8) Dressing with chloramphenicol 5% ointment. (9) Medication from the first postoperative day with homatropine 1% and dexamethasone soluble 0·1% with neomycin 0·5% drops for 6 weeks. All the operations were performed under the surgical microscope.

Results

From May 1974 through May 1977, 70 eyes of 56 patients were subjected to trabeculectomy; 28 were affected by chronic open-angle glaucoma, 39 by chronic angle-closure glaucoma (including acute exacerbation of angle-closure glaucoma), and 3 by secondary glaucoma (2 due to uveitis and 1 due to central vein thrombosis). Five eyes out of 70 were subjected to combined trabeculectomy and cataract extraction.

The follow-up period was 1 to 3 years. Table 1 shows the variations of the IOP during the postoperative period. Out of 70 eyes at the last follow-up 51 (73%) had a normal IOP without medication, while 17 (24·3%) had a normal IOP with medication and 2 had an uncontrolled IOP.

Fig. 1 shows the IOP of 25 eyes on the day of the operation. Their IOP was raised on the second postoperative day. This number represents 35·7% of the operated eyes. Out of 25 eyes with raised IOP on the second postoperative day 11 belonged to the chronic open-angle group and 13 to the chronic angle-closure group. One eye was from the combined trabeculectomy and cataract extraction group.

Table 2 shows the complications we have recorded

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in the 70 cases. They were hyphaema, iridocyclitis, development of slight lens opacities, flat anterior chamber, and iris bombé.

Discussion

We agree with Wilson's (1977) opinion that trabeculectomy is a successful operation in patients with chronic open-angle glaucoma and chronic angle-closure glaucoma. Its efficiency in cases of secondary glaucoma is only partial, and our only case of thrombotic glaucoma was a failure.

Trabeculectomy is free of major operative and postoperative complications (Watson and Barnett, 1975). Many clinicians report in their studies that in comparison with the other filtering procedures trabeculectomy has only a few minor complications (Schwartz *et al.*, 1976). They were rare in our cases.

The most interesting result of this study is the rise of the IOP on the second postoperative day.

Table 1 *Range of IOP during the post-trabeculectomy period, in mmHg*

<table>
<tr><th rowspan="2"></th><th rowspan="2"><i>Immediately after operation</i></th><th rowspan="2"><i>One month after operation</i></th><th colspan="2"><i>Last recordings in patients</i></th></tr>
<tr><th><i>Without medication No. of eyes</i></th><th><i>With medication No. of eyes</i></th></tr>
<tr><td></td><td></td><td></td><td>21</td><td>7</td></tr>
<tr><td>Chronic open-angle glaucoma (28 eyes)</td><td>0–40</td><td>0–32</td><td colspan="2">10–21</td></tr>
<tr><td></td><td></td><td></td><td>29</td><td>10</td></tr>
<tr><td>Chronic angle-closure glaucoma (39 eyes)</td><td>0–50</td><td>0–21</td><td colspan="2">12–20</td></tr>
<tr><td></td><td></td><td></td><td>1</td><td>2</td></tr>
<tr><td>Secondary glaucoma (3 eyes)</td><td>8–25</td><td>8–34</td><td colspan="2">15–35</td></tr>
</table>

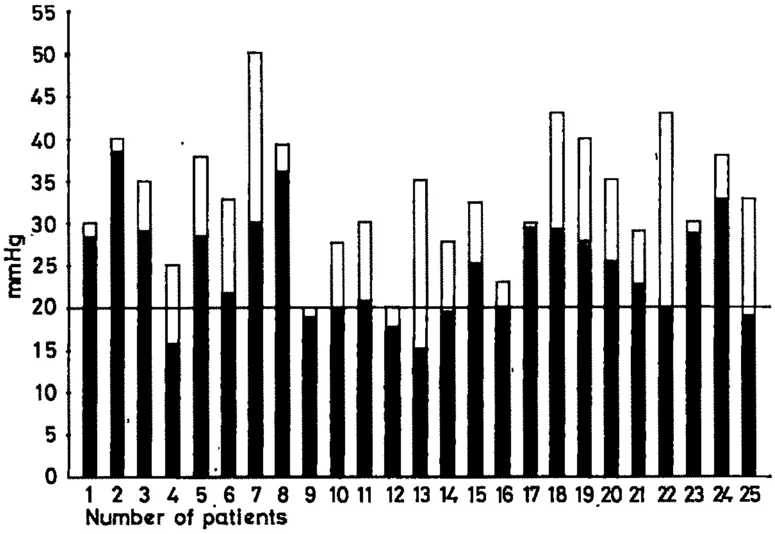

Fig. 1 *Intraocular pressures before and after trabeculectomy in 25 patients. Black = IOP on day of operation. White = IOP 2 days after trabeculectomy*

Table 2 *The postoperative complications recorded in the 70 cases*

Type of glaucoma	*Type of complications*			
	Hyphaema	*Iridocyclitis*	*Slight lens opacities*	*Flat anterior chamber and iris bombé*
Chronic open-angle glaucoma	3	0	5	0
Chronic angle-closure glaucoma	3	2	3	2
Secondary glaucoma	0	0	1	2

This raised IOP lasted from 2 to 7 days and did not affect in any way the final result of the operation, in contrast with Portney's study (Portney, 1977). We presume that the increase of the IOP was caused by our technique of tightly closing the scleral flap by 5 sutures (Fechner, 1975). These sutures do not prevent the formation of a fine filter a few days after the operation, which reduces the IOP to normal. On the other hand the sutures prevent the formation of a flat anterior chamber, which was present in 4 cases only and disappeared after 2 days. The rise of the IOP did not cause an iris reaction stronger than in patients without IOP elevation.

Our follow-up is not as long as the follow-up of Wilson (1977), but he showed too that the number of uncontrolled cases does not increase significantly after 1 year of follow-up (40 to 44 eyes).

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Amblyopia: the need for a new approach?

R. M. INGRAM
From the Kettering and District General Hospital, Kettering

SUMMARY Follow-up of a series of 221 children identified by the present methods of screening, and presenting consecutively with squint and/or amblyopia, shows that there has been no demonstrable improvement in the overall incidence and severity of amblyopia 3 or more years later. A new approach to the problem is required, and this might be based on the identification and treatment of amblyopia during the 'sensitive period'.

A primary purpose of treating childhood visual disorders is reduction of the incidence and severity of amblyopia. This is a review of the overall results of treating an unselected sample of children. Although limited in content, they clearly point to the need for a fundamental change in our management of the problem.

Patients and methods

The children surveyed are an unselected group who attended the ophthalmic clinics of the Kettering district for the first time between 1 November 1971 and 31 October 1972. Their presenting features have already been reported (Ingram, 1977).

Amblyopia was recorded as the difference between the visual acuity of a pair of eyes when this was measured on a Linear Sheridan-Gardiner or Snellen chart. The total number of attendances for each child were also recorded on a master chart.

Results

Table 1 shows the number of children who were known to have amblyopia in each age group at the time they presented. In some cases, recorded as (?) amblyopia, there were grounds for suspecting amblyopia although the actual acuities were not known.

Table 2 shows the number of children and their amblyopia 3 or more years later. For ease of comparison they are recorded according to the age at which they presented. There are 5 more children in this Table, because 2 were 'missed' off the original charts which formed the basis for Table 1 and other publications (Ingram, 1977; Ingram *et al.*, 1977), and 3 children were originally thought to be normal but were eventually found to have esotropia and/or amblyopia. Those who were considered too old for treatment when they presented were not re-examined, and it has been assumed, perhaps wrongly, that their vision has not altered significantly.

Table 1 *Amblyopia at the time the children presented*

Age of presentation *Amblyopia:*	*0*	*<1*	*<2*	*<3*	*<4*	*<5*	*5+*	*?*	*Total*
0–1	2	—	—	—	—	—	1	6	9
1–2	3	—	—	—	—	—	—	11	14
2–3	2	—	—	2	—	—	1	11	16
3–4	9	5	2	2	—	—	5	2	25
4–5	6	—	3	1	—	—	1	1	12
5–6	14	5	6	6	2	3	6	6	48
6–7	4	4	6	5	—	1	3	5	28
7–8	5	3	1	4	2	—	2	3	20
8+	10	6	5	10	10	2	5	1	49
Total	55	23	23	30	14	6	24	46	221

We knew the initial and final visual acuity of 91 of those children who attended reasonably regularly for treatment. The details of these children have been reported (Ingram *et al.*, 1977) (Tables 1 and 2), but they are summarised in Table 3.

Discussion

Chavasse (1932) said: 'I think the time has come for us to admit, to ourselves at all events, that the treatment of these cases is, in the bulk, unsatisfactory'. He was talking about squint, but the same could also be said about our treatment of amblyopia. A large number of outpatient attendances have resulted in no overall reduction in the incidence or severity of amblyopia in this district. Nobody could

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Table 2 *Amblyopia 3½ years after initial presentation*

Age of presentation	*Amblyopia:*	*0*	*<1*	*<2*	*<3*	*<4*	*<5*	*5+*	*?*	*Total*	
0–1		2	1	1	—	—	—	2	5	11	2 missed off original
1–2		2	—	1	4	—	1	1	6	15	1 developed squint
2–3		4	2	—	2	1	3	4	—	16	
3–4		6	4	6	3	2	4	—	1	26	1 extra found to be amblyopic
4–5		7	—	3	1	—	1	—	—	12	
5–6		4	4	17	9	4	6	4	1	49	1 missed off original
6–7		2	6	6	5	2	—	4	3	28	
7–8		4	5	1	4	1	2	1	2	20	
8+		11	6	4	9	11	2	5	1	49	
Total		42	28	39	37	21	19	21	19	226	

Table 3 *Initial and final visual acuity*

Amblyopia:	*0*	*<1*	*<2*	*<3*	*<4*	*<5*	*5+*
Initial	27	11	15	17	4	2	15
3+ years later	13	14	26	18	5	9	6

21 had >3 lines of amblyopia initially, and 20 had this degree of amblyopia 3+ years later

claim that identification and treatment of these particular children has been effective or efficient, and it is important not to overlook the distress and inconvenience caused to individual parents and children by unnecessary hospital attendances.

On the other hand we cannot simply dismiss our present methods of treatment because we do not know how many of those children presenting now would have deteriorated to severe (secondary?) amblyopia if they had not been treated. This is our dilemma: Occlusion is the standard treatment for amblyopia, but we use it more in the hope that it will reduce amblyopia than in the certain knowledge that it will cure. In practice the problem is when to stop it.

We found that occlusion consistently reduced the amount of amblyopia in only a small group of 15 of these children, all of whom presented with severe amblyopia and none of whom were cured (Ingram *et al.*, 1977). We have suggested that it is effective only in the reduction of amblyopia secondary to relatively long-standing squint (Ingram *et al.*, 1977). More specifically, we seem to be incapable of improving what we have called 'primary' amblyopia. Possibly this is because (see, for example, Breinin (1973)) occlusion is most often used after the end of the 'sensitive period' identified in animals (Hubel and Wiesel, 1970; Blakemore and van Sluyters, 1974). If this is so, then we need to clarify the duration of the 'sensitive period' in man in order that treatment may be given at a time when it might be effective.

Chavasse (1932) also said: 'A satisfactory understanding of the nature of squint is of primary importance'. The animal experiments started by Hubel and Wiesel may provide this, but whether squint and amblyopia are the result of an inborn neurological abnormality or an environmental factor such as blurred vision during the sensitive period (Whitteridge, 1977) is still disputed.

The fact that these children made 1487 return attendances to the clinic is a measure of the time and money spent in the doubtful improvement of a condition that had probably been established long before any defect was identified. Clearly, there is scope here for redistribution of resources in the search for more effective management of the problem. Chavasse (1932) regarded it as 'A problem of the public health', and, if this is correct, we must ultimately aim to devise a means of prevention. Screening is regarded as the key to this. For clinicians the problem is when should we screen and what should we look for?

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British Journal of Ophthalmology, 1979, **63**, 238–242

Refraction as a means of predicting squint or amblyopia in preschool siblings of children known to have these defects

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SUMMARY 215 preschool siblings of children presenting with squint/amblyopia were screened by refraction after cycloplegia. The presence of +2·00 or more D of spherical hypermetropia in both eyes, or +1·00 or more D sphere or cylinder of anisometropia was significantly associated (P=0·0779%) with that child being identified 2+ years later as having either squint or amblyopia or both. Astigmatism of +1·50 or more D in either eye was significantly associated with anisometropia (P=0·000 0013%). If bilateral hypermetropia of +2·00 or more DS and/or +1·50 or more D of astigmatism in either eye had been taken as criteria for abnormality (ignoring anisometropia), there was a more significant association (P=0·0025%) between refraction and squint/amblyopia in these siblings. Such a child had 4 times more chance of having a visual defect than one who had no error of refraction when screened. These findings suggest that an environmental factor such as blurred vision may be relatively more important as a cause of squint/amblyopia than a genetically determined neurological abnormality.

Thomson (1924) and Chavasse (1932) suggested preventive treatment for squint without specifying which children required it. Bruckner, as reported and confirmed by Seba (1970), probably tried to predict which children were going to squint but did not refer this to a method of prevention. His test was, to say the least, vague, but we think that he was possibly identifying children with abnormal refractions. Kramar (1973), however, looked specifically for a test that might enable us to predict, and she suggested that refraction might offer a better chance of doing this than examination of other physical parameters. This offered the opportunity of a genuinely new approach to squint and amblyopia because it happened directly to lead to treatment that could possibly be preventive, that is, that suggested by Thomson (1924) and Chavasse (1932). Ingram (1977) enlarged on this by pointing out the advantages that an objective test had over new or improved subjective tests, particularly with a view to identifying the 'non-squinting' amblyopes as well as those who were going to squint.

Refraction without cycloplegia has been used before to screen schoolchildren for defective vision (Tyser and Letchworth, 1949; Hirsch, 1950; Jevons, 1954). It has also been recommended, after cycloplegia, as part of a full ocular examination of children at birth (Seba, 1974), aged 3 to 6 months (Winstanley, 1966) and aged 3+ years (Abeloos, 1970; Litvinova *et al.*, 1964). So far as we are aware, nobody has yet explored the possibility of using cycloplegic refraction actually to predict which children will be identified later as having squint and/or amblyopia.

The obvious way to test Kramar's (1973) suggestion would be to try it on a group of children unusually liable to have squint and/or amblyopia, for example, preschool siblings of those who actually present with these conditions. We report a follow-up study of 215 siblings reviewed 2+ years after they were first screened by retinoscopy following cycloplegia with cyclopentolate (Cyclogyl 1%).

A future publication (Ingram *et al.*, 1979) reports the findings of follow-up of 186 children seen in a pilot study designed to find out if it would be practical to screen routinely 1-year-old children by refraction. Both samples have been assessed by the same criteria to enable comparison to be made.

Sample of children

215 preschool siblings of children who presented with squint and/or amblyopia were screened during

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a 3-year period 1971–74. One of us (R. M. I.), who recorded the findings of these children as they were screened, is conscious of the fact that the 'record-keeping' was not as diligent as it might have been. Therefore we cannot claim that the 215 children reported here were a truly consecutive series, because: (1) Some preschool siblings were not brought for screening. (2) The records of the findings from some siblings were mislaid. We think that there were not more than 10 of these and that all were found to have a 'normal' refraction when screened. We do not think that these deficiencies alter our conclusions. Unfortunately, however, we cannot make any observations on what appears to be a high incidence of refractive errors in siblings of children who present with squint and/or amblyopia.

Methods

Retinoscopy of each child was performed after cycloplegia with cyclopentolate (Cyclogyl 1%) drops. The refraction in 2 meridia of each eye was recorded on the principles suggested by Ingram (1977). All the refractions were performed by the same person (R. M. I.).

At the time of screening we considered that +2·00 DS of hypermetropia in both eyes was a significant amount of hypermetropia, and that +1·00 or more DS or +1·00 or more D cyl. difference between the two eyes was a significant amount of anisometropia, and that children with such refractions should be regarded as 'abnormal'.

A number of children were periodically reviewed, and 35 of them were treated with spectacles at some time before their final assessment.

Final assessment

An attempt was made to review all the children 2+ years after their initial screening. We have chosen 3 criteria on which to assess whether an individual child's vision was normal or abnormal, because they could also be applied to the simultaneous assessment and reporting of the pilot study of children screened at the age of 1 year and reviewed at the age of 3½ years (Ingram *et al.*, 1979): (1) Esotropia or exotropia, detectable by the cover test. (2) Visual acuity of <6/12 in either eye, measured only with the Linear Sheridan-Gardiner or Snellen tests. (3) The difference between the corrected visual acuity of the 2 eyes of >1 line, again measured only with the Linear Sheridan-Gardiner or Snellen tests.

In some children we found difficulty in interpreting the 4 dioptre prism test for microtropia, and we have not therefore included this as a criterion of abnormality. However, where we felt sure that there was a microtropia we have recorded it but made no further observations.

We accept that treatment of some of the children before a visual abnormality was detected has complicated the final assessment, particularly in relation to the recording of visual acuity. If the visual acuity was 6/12 or better with a spectacle correction, we have counted the acuity as 'normal' unless there was >1 line of difference between the 2 eyes. Manifest squint with or without spectacles has been counted as 'abnormal'.

Thirty-one children did not attend again for re-assessment, and 22 others had apparently moved from our area. Thus, 162 children have been re-assessed. They were divided into 2 groups according to whether they did or did not have an 'abnormal' refraction when they were screened. We have not published full details of the refractions and vision of all the individual children, but we would be happy to supply photocopies of them to interested inquirers.

Summary of findings

The visual findings from these children can be summarised and statistically analysed in terms of whether detection of an 'abnormal' refraction at the time of screening was significantly associated with a child being eventually found to have normal or abnormal vision. Thus, detection of bilateral spherical hypermetropia and/or anisometropia was significantly associated with the future detection of squint and/or amblyopia (Table 1).

Refractions other than bilateral hypermetropia and/or anisometropia could be considered in retrospect as being abnormal. For example, if +1·50 D of astigmatism in either eye had also been regarded as 'abnormal', even when there was no significant hypermetropia or anisometropia, such a refraction would have been significantly associated with the later detection of squint and/or amblyopia (Table 2).

If anisometropia had been ignored, and the criteria for 'abnormality' taken as hypermetropia of +2·00 or more D in both eyes and/or +1·50 or

Table 1

	Normal vision	*Squint/amblyopia*	*Total*
Normal refraction	99	14	113
Abnormal refraction	31	18	49
Total	130	32	162

$\chi^2 = 11{\cdot}29$, P = 0·0779%

Table 2

	Normal vision	*Squint/amblyopia*	*Total*
Normal refraction	94	11	105
Abnormal refraction	36	21	57
Total	130	32	162

$\chi^2=14\cdot58$. P=0·0134%

Table 3

	Normal vision	*Squint/amblyopia*	*Total*
Normal refraction	98	11	109
Abnormal refraction	32	21	53
Total	130	32	162

$\chi^2=17\cdot80$. P=0·0025%

more D astigmatism in either eye, such a refraction would have been slightly more significantly associated with the later detection of squint and/or amblyopia (Table 3).

OBSERVATIONS ON THE POSSIBLE CONSEQUENCES OF OUR TREATING 12 OF THE CHILDREN

We can only guess at the effects of the treatment we gave to some of these children, but it is reasonable to suppose that if 8 children had not been identified and treated they would have been detected later by the school screening programme. All 8 had +2·00 D or more astigmatism in 1 or both eyes at the age of 5 years or later. If they had not been screened, it is reasonable to suppose that we would have identified 29 out of the 40 children with a visual abnormality, that is, 72%. It is possible that 4 others would also have presented with a visual defect if they had not also been screened and treated.

ANISOMETROPIA AND ASTIGMATISM

We also record for future reference the association in this sample of preschool siblings between the presence of anisometropia on the one hand and astigmatism of +1·50 or more D in either or both eyes on the other hand (Tables 4 and 5).

Discussion

PREDICTION BY REFRACTION OF SIBLINGS

In this series of preschool siblings of children presenting with squint and/or amblyopia there is a statistically significant relationship (Table 1, P=0·0779%) between the presence of what we have regarded as significant (Ingram, 1977) amounts of hypermetropia and/or anisometropia and the future identification of squint or defective visual acuity in that sibling. However, only 56% (Table 1) of those who eventually had a visual defect were predicted on the basis of these refractions. This compares with 72 ±3% of children who were found to have hypermetropia and/or anisometropia at the time they presented with squint and/or amblyopia (Ingram, 1977) and a prediction rate of 73% of children screened in our pilot study of 1-year-olds (Ingram *et al.*, 1979).

Since we started this particular investigation, the entity of meridional amblyopia has been identified (Mitchell *et al.*, 1973) and accepted as a form of stimulus deprivation amblyopia (Noorden, 1974). A significant association between astigmatism of +1·50 D or more in either or both eyes and what we have regarded as significant amounts of anisometropia was noted in this sample of children (Table 4, P=0.000 0013%) among 1-year-old children (Ingram, 1979) and in children at the time they present with a visual problem (Ingram, unpublished). If we had taken +1·50 D or more astigmatism in either eye, in addition to bilateral hypermetropia and/or anisometropia, and regarded all 3 as 'abnormal', the significance of any 1 or more of these refractions being associated with the future identification of squint/amblyopia increases (Table 2, P=0·0134%). If, however, we had ignored anisometropia and just selected bilateral hypermetropia of +2·00 or more DS and/or astigmatism of +1·50 or more D in either eye as abnormal criteria, we would have had an even higher statistical association (Table 3, P=0·0025%), and we would have predicted abnormal vision in 66% of those

Table 4 *Anisometropia and astigmatism (astigmatism in either or both eyes)*

	No Aniso.	*Aniso.*	*Total*
0 to +1·25 D cyl.	179	7	186
+1·50 or more D cyl.	16	13	29
Total	195	20	215

P=0·000 0013%

Table 5 *Anisometropia and astigmatism (astigmatism in either or both eyes)*

	No Aniso.	*Aniso.*	*Total*
0 to +0·75 D cyl.	168	2	170
+1·00 or more D cyl.	27	18	45
Total	195	20	215

P=0

children eventually found to have a visual defect.

In some respects it is unfortunate that we treated 35 of these children with spectacles. We believe that if 8 of them had not been treated they would eventually have been found to have defective vision, and we would have predicted 72% of those who should eventually present with an abnormality. There is therefore strong circumstantial evidence to support Kramar's (1973) suggestion.

Absence of hypermetropia or astigmatism (or anisometropia) at the time a preschool sibling is seen at the age of 1 year or later does not preclude future identification of squint and/or amblyopia: such a child had a 10% chance of later being found to have squint and/or amblyopia. On the other hand, if that child had hypermetropia or astigmatism, he/she had a 2 in 5 chance of being found later to have a visual defect, and this is 4 times higher than it would have been if no abnormality of refraction had been found.

AETIOLOGY OF SQUINT AND/OR AMBLYOPIA

It seems that the cause of squint and/or amblyopia could be either an environmental factor such as blurred vision affecting a system of neuronal connections between retina and cortex that is developing during the first few months of life (see, for example, Ikeda and Tremain, 1978; Blakemore and Eggers, in press) or a genetically determined inborn neurological abnormality, as suggested by Wiesel and Hubel (1974). Alternatively, there could be both a genetic and an environmental factor (see Whitteridge, 1977) acting separately or coincidentally. The species of experimental animal may be important, because in the kitten, whose eye is 'immature' at birth, the process of development may be relatively more important and therefore the neuronal connections may be more easily distorted by environmental factors than is the case in higher mammals, for example, the lamb. Recent work shows that vision develops rapidly during the first 3 months of the human infant's life, which suggests that the neuronal connections may not be as well developed as in the lamb (Atkinson *et al.*, 1977).

The presence of identical squint in uniovular twins has been cited in favour of the genetic basis of squint (Whitteridge, 1977). In this sample, 1 such pair of twins developed squint in the absence of any refractive error when they were screened. Nevertheless, uniovular twins often have identical refractions (Sorsby and Benjamin, 1973; Weekers *et al.*, 1956), although this is not inevitable (Kvapilikova, 1970), and there is other evidence that refraction is inherited (Waardenburg, 1963; Sorsby *et al.*, 1966). This pair of twins were 2 years old when screened, and the absence of a refractive error at this age does not preclude the possibility that they had an abnormal refraction when they were younger.

Preschool siblings of children known to have squint or amblyopia might be expected to have a significant risk of having a genetically determined neurological abnormality. Nevertheless, in this sample there is a highly significant association between a refractive error and the eventual identification of a visual defect. This is compatible with other observations, as follows:

(1) There was a significant association between refractive errors and visual defect ($P<0{\cdot}01$) among the subjects in the 20 families specifically selected by Kramar (1973) because of the distribution of squint/amblyopia within them. (2) Among children presenting before the age of 2 years with squint/amblyopia the association of a refractive error was more significant than the reported incidence of a family history (Ingram, 1973). (3) In a sample of children of all ages presenting with possible visual problems the association of a refractive error with squint/amblyopia was itself significantly higher ($P<0{\cdot}05$) than the (already significant) incidence of a family history (Ingram, 1977).

Taken together, these observations suggest that, in man, an environmental factor such as blurred vision caused by an uncorrected refractive error may be a more important factor causing squint and/or amblyopia than an inborn neurological lesion. If this is so, attention could be directed towards the search for refractive errors of sufficient magnitude to cause blurred vision during the sensitive period. If it was ever possible to demonstrate successful prevention of squint and/or amblyopia by creating clear vision throughout this period, we would have gone some way towards deciding the relative importance of the genetic and developmental theories.

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Screening for refractive errors at age 1 year: a pilot study

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SUMMARY Cycloplegic refraction of 1-year-old children is technically possible and is acceptable to mothers as a method for screening children for visual defects. The range of refractions found in a sample of 186 1-year-old children is reported. Prediction of which children are significantly at risk for squint and/or amblyopia is possible on the basis of refractions at age 1 year according to the criteria selected for an 'abnormal' refraction. Bilateral hypermetropia and/or astigmatism or anisometropia at age 1 year was significantly ($P<1$ in 10 000) associated with a child eventually being found to have squint or amblyopia. Both the age of screening and the criteria of abnormality will probably need modification. +2·50 or more D hypermetropia in any one meridian of either eye at age 1 year was even more significantly ($P = 0{\cdot}000\,000\,05\%$) associated with squint and/or amblyopia. The possibility that meridional hypermetropia could be the basic defect in squint and amblyopia is discussed.

Thomson (1924) believed that 'our object and ideal should be the correction of the refractive error before the squint occurs', and Chavasse (1932) thought that if this was done 'before the time when the infant's visual reactions assume primatial characteristics, it would prevent the development of squint'.

However, identification of children in whom squint might reasonably be predicted must precede any preventive treatment, and Kramar (1973) concluded that refraction might be the best way of doing this. Screening should include children not known to have a family history of squint or amblyopia and must certainly be carried out before the age of 3 years, because this is the first peak age when children present with esotropia (Ingram 1977a). The age of 1 year was chosen for this study simply because we thought it would be technically easier to refract at that age rather than later. It remains to be seen, however, whether this is young enough, that is, within the sensitive period.

The study was designed (1) to find out if cycloplegic refraction of 1-year-old children was technically possible and acceptable to parents, and, if so, (2) to determine the range of refractions that might be found at this age.

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We have delayed reporting our findings in order to have some indication of how effective the procedure might be in terms of predicting visual problems. This meant that we had to wait until the children had attained the age of 3½ years at least. Since this was a direct test of Kramar's (1973) suggestion, the results could be published coincidentally with another test of this principle in preschool siblings of children known to have squint and/or amblyopia (Ingram and Walker, 1979).

Sample of children

We visited the premises of 2 general medical practices at the same time as 1-year-old children were attending for immunisation. Since the children were 'called' by a computer for immunisation, we knew exactly how many children could potentially have been screened. 72% attended, and the mother of each of these children was offered the opportunity to have her child's eyes 'screened'. Only 4 of these declined, and overall 69% of those theoretically available were examined—a total of 186 children.

Methods

Retinoscopy of each child was performed 30 minutes after several drops of Cyclogyl 1% had been instilled into both eyes and the refraction recorded according to the principles suggested by Ingram

Table 1 *Refraction of children at age 1 year*

Astigmatism	*Sphere*													
	← −*1·25*	−*1·00* −*0·75*	−*0·50* −*0·25*	*0* +*0·25*	+*0·50* +*0·75*	+*1·00* +*1·25*	+*1·50* +*1·75*	+*2·00* +*2·25*	+*2·50* +*2·75*	+*3·00* +*3·25*	+*3·50* +*3·75*	+*4·00* +*4·25*	+*4·50* →	*Total*
0 +0·25	2	2	11	16	17	8	6	2	2	1	2			69
+0·50 +0·75		1	8	19	14	5	5	3		3				58
+1·00 +1·25	1+2A		7	4	10	4	3	2	0+1A					34
+1·50 +1·75		1	3+1A	2	0+2A	2			0+1A				1	13
+2·00 +2·25		3	1	0+1A										5
+2·50 +2·75	0+1A		1	0+1A										3
+3·00 ↓	0+3A													3
Total	9	7	32	43	43	19	14	7	4	4	2	0	1	185

A = child with anisometropia

(1977b). If the pupils were not dilated after 15 minutes, or if the refraction seemed to vary during retinoscopy, more drops of Cyclogyl were instilled and retinoscopy carried out 30 minutes after this. All the refractions were performed by the same person (R. M. I.).

Those children found to have 'abnormal' refractions were followed up. Some of them were given spectacles at a later date, and we accept that this was not a wise or correct method of handling the problem in the absence of an established visual abnormality, such as squint or defective visual acuity.

Final assessment

An attempt was made to review all the children at the age of 3½ years. Visual acuity was recorded then or as soon as possible after that, using the Linear Sheridan-Gardiner test. The criteria for what was regarded as normal or abnormal vision were the same as those chosen for the assessment of preschool siblings (Ingram and Walker, 1979), that is, a child was assessed as 'abnormal' if there was any one or more of the following findings: (1) esotropia or exotropia detectable by the cover test; (2) visual acuity of < 6/12 in either or both eyes, with correction if necessary; (3) a difference of > 1 line between the acuity of the 2 eyes.

We accept that the choice of these criteria could be criticised, but recording of visual acuity in children of this age is not always reliable; for example, a child might admit to seeing only 6/12 and yet have normal acuity or amblyopia. More than one attendance was necessary for some of the children. Also, we recognise that it is possible for a child of 3½ to show no signs of strabismus and yet later present with an (accommodative) esotropia. This happened with 2 children. Both were initially credited with 'normal' vision but reappeared at 5 years of age with a manifest left esotropia and have been recorded as 'abnormal'.

Findings

It was impossible to refract or assess the vision of 1 child because of gross congenital abnormalities. The refractions of 185 children at age 1 year are shown in Table 1, where they are recorded on the basis of the spherical refraction of the more myopic or emmetropic eye and the maximum amount of astigmatism (recorded as +cylinders) found in either eye. *A* indicates a child who had what we have regarded as a 'significant' amount of anisometropia, that is, +1·00 DS and/or +1·00 D cyl. difference between the refraction of the 2 eyes.

Fifteen of these children did not reattend for assessment at age 3½ and 17 others had moved away from this area. Thus, we have re-examined 153 of the original sample of children. We were unable to assess the vision of 4 of these and the refraction of 5 of them.

The refractions of the individual eyes of the 148 children who were refracted on both occasions are

Table 2 *Refraction of individual eyes of 148 children at age 1 year*

Astigmatism	*Sphere*													
	← −1·25	−1·00 −0·75	−0·50 −0·25	0 +0·25	+0·50 +0·75	+1·00 +1·25	+1·50 +1·75	+2·00 +2·25	+2·50 +2·75	+3·00 +3·25	+3·50 +3·75	+4·00 +4·25	+4·50 →	*Total*
0 +0·25	4	4	19	19	32	14	12	3	5	3	3	2		120
+0·50 +0·75		2	17	20	23	7	9	2	3	3	2			88
+1·00 +1·25	2+1A	1	8	6	15	12	4	3		0+1A				53
+1·50 +1·75		1	6+1A	7	0+1A	2	0+1A		0+1A				2	22
+2·00 +2·25	1	3		2+1A										7
+2·50 +2·75	0+1A		1	0+1A										3
+3·00 ↓	0+3A													3
Total	12	11	52	56	71	35	26	8	9	7	5	2	2	296

A = an anisometropic eye

Table 3 *Refraction of individual eyes of 148 children repeated at age 3½ years*

Astigmatism	*Sphere*													
	← −1·25	−1·00 −0·75	−0·50 −0·25	0 +0·25	+0·50 +0·75	+1·00 +1·25	+1·50 +1·75	+2·00 +2·25	+2·50 +2·75	+3·00 +3·25	+3·50 +3·75	+4·00 +4·25	+4·50 →	*Total*
0 +0·25	4	2	10	29	60	56	13	9	2+1A	5+1A	1	4	3	200
+0·50 +0·75		1	4	15	28	15	3+1A		2	1+2A			1	73
+1·00 +1·25				2	1+1A	1	2		1					8
+1·50 +1·75			3+2A	0+1A	1		2	0+1A					1	11
+2·00 +2·25			0+1A	1+1A										3
+2·50 +2·75													0+1A	1
+3·00 ↓														0
Total	4	3	20	49	91	72	21	10	6	9	1	4	6	296

A = an anisometropic eye

summarised, on the basis described above, at age 1 year (Table 2) and 3½ years (Table 3). *A* indicates an anisometropic eye. Of the 149 children whose vision we assessed 7 had esotropia, 1 had exotropia, 5 had amblyopia and microtropia, and 2 had amblyopia without a microtropia.

We have not published the refractions and visions of all the individual children, but we would be happy to supply photocopies of the details to interested enquirers.

Discussion

There is no doubt that it is technically possible to screen (by refraction after cycloplegia) children as young as 1 year old. The procedure seemed to be acceptable to parents (96% of those to whom it was offered accepted), and later experience has confirmed this. As most children now have their hearing checked at the age of 9 months, it is natural that their vision should be screened at about the same age.

RANGE AND INCIDENCE OF REFRACTIONS FOUND AT AGE 1 YEAR

A curve representing the range of refractions found at age 1 year was roughly similar to that of Fabian (1966), who refracted children between the ages of 1 and 2 years, and it is similar in shape to that found in another sample of 1-year-old children refracted after atropine cycloplegia (Ingram and Barr, 1979b). It is more peaked and has a narrower spread than similar curves representing the refractions of newborn children (Cook and Glasscock, 1951; Graham and Gray, 1963; Goldschmidt, 1969).

The incidence of spherical hypermetropia and/or anisometropia (15·6%) is slightly less than was expected (Ingram, 1977b). The incidence of hypermetropic astigmatism was 12·9%, and this may be important. We were surprised to find that the axis of astigmatism, when recorded as +cylinders was in the (nearly) horizontal axis as often as it was in the (nearly) vertical axis (Table 5).

VISUAL ASSESSMENT AT 3½ YEARS OF AGE

We are uncertain about the vision of 4 children, and 1 other child had such gross congenital abnormalities that we thought he should be excluded altogether, but we have been able to assess the vision of 149 of the original sample. Fifteen of these (10%) have shown signs of squint and/or amblyopia, and possibly one or two others may yet develop manifest squint. We expected to find an incidence of about 7%. The slightly higher percentage might be due to our sample being atypical of the population, but we cannot prove or disprove this.

Table 4 *Summary of findings of refractions at age 1 year*

Number of children with bilateral hypermetropia +2·00 or more DS	= 18 =	9·7%
Number of childred with astigmatism +1·50 or more D in one or both eyes	= 24 =	12·9%
Number of children with anisometropia	= 13 =	7·0%
Number of children with bilateral hypermetropia and/or anisometropia	= 29 =	15·6%

Table 5 *The axis of astigmatism when this was recorded as +cylinders*

	Horizontal	*Vertical*
+0·50/+0·75 D	57	55
+1·00/+1·25 D	27	32
+1·50 or more D	27	10

Table 6 *Possibility of predicting visual outcome: hypermetropia and/or anisometropia at age 1 year*

	Normal vision	*Amblyopia*	*Total*
Normal refraction	119	4	123
Abnormal refraction	15	11	26
Total	134	15	149

$\chi^2 = 31·97$. DF = 1. P = 0·000 0015%

POSSIBILITY OF USING REFRACTION AS A MEANS OF PREDICTING SQUINT/AMBLYOPIA

As with the sample of preschool siblings (Ingram and Walker, 1979) we have found a highly significant association between the identification of bilateral hypermetropia and/or anisometropia and the future detection of squint and/or amblyopia (Table 6, P=0·000 0015%). Again, it is true that we have not predicted correctly in the case of all the children. In fact we have predicted only 11 out of the 15 recorded as 'abnormal', that is 73%.

There are 5 possible explanations why we have not predicted more accurately: (1) Cyclogyl did not give sufficient cycloplegia (see Ingram and Barr, 1979b); (2) the refraction was incorrectly carried out; (3) the criteria for an abnormal refraction were wrongly selected (see alternatives later in this paper); (4) the refractions at age 1 year do not accurately reflect the refraction during the crucial part of the sensitive period, if this is earlier in life; (5) the basic cause of squint/amblyopia is not a refractive error leading to blurred vision during the sensitive period but a genetically determined neurological abnormality, as suggested by Wiesel and Hubel (1974). At present we think that (4) is the probable explanation.

ANISOMETROPIA

We have been interested in anisometropia since Ikeda and Wright (1975) suggested that it could cause stimulus-deprivation amblyopia if it was present during the sensitive period. Although he did not define what he meant by anisometropia, Lukaszewicz (1972) identified it at age 1 year, but Kubistova (1968) failed to find anisometropia at age 7 months and thought it 'appeared' between then and 3½ years. If this was so, it would, of course, eliminate Ikeda and Wright's (1975) hypothesis.

We found that 7·0% of our children had anisometropia at age 1 year, but, what is more important, we found that anisometropia both 'disappeared' and 'appeared' between the ages of 1 and 3½ years. Of the 12 children who had anisometropia at age 1 year 7 no longer had it at age 3½. None of these children had amblyopia, and at first sight this argues against Ikeda and Wright's (1975) theory, but we do not know whether they were anisometropic earlier in life, for example, during the first 3 months, and only 2 of them had significant hypermetropia (+2·50 D) in any one meridian at age 1 year (see later). Eight children who did not have anisometropia at age 1 year had anisometropia at 3½. Five of these did not have amblyopia, and in clinical practice anisometropia is not invariably associated with amblyopia. Only 2 of them had +2·50 D in any one meridian (see later). We do not know whether the 3 who were amblyopic had anisometropia before the age of 1 year, but in fact 2 of the 3 had +2·50 D in one or more meridia at age 1 year (see later).

CRITERIA FOR AN ABNORMAL REFRACTION

Bilateral hypermetropia and/or anisometropia were originally selected as criteria for an abnormal refraction because these are the refractions traditionally regarded as being associated with squint/amblyopia.

It would have been foolish not to have looked, in retrospect, at other possible refractions that could be regarded as abnormal. Mindful of the acceptance (von Noorden, 1974) of meridional amblyopia (Mitchell *et al.*, 1973) as a form of stimulus-deprivation amblyopia, and thinking that anisometropic amblyopia could also be a form of stimulus-deprivation amblyopia, we looked for and found a very close association between astigmatism and anisometropia in 1-year-old children (Ingram, 1979). This finding was confirmed in preschool siblings of children who presented to us with squint/amblyopia (Ingram and Walker, 1979) in this series of children both at age 1 and 3½ (Ingram and Barr, 1979a), and in children as they present with visual defects (unpublished data). This led us to consider hypermetropia and/or astigmatism of +2·00 or more D in either eye at age 1 year as being a possible pointer to identifying children who will eventually present with squint and amblyopia, and there is a significant association between these two conditions (see Table 7, P=0·000 036%).

Table 7 *Possibility of predicting visual outcome: hypermetropia and/or astigmatism +2·00 or more D*

	Normal vision	*Amblyopia*	*Total*
Normal refraction	119	5	124
Abnormal refraction	15	10	25
Total	134	15	149

χ^2 = 25·89. DF = 1. P = 0·000 036%

Table 8 *Meridional hypermetropia at age 1 year and prediction of squint/amblyopia*

(*a*) +2·00 or more D in any one (or more) meridian

	Normal vision	*Amblyopia*	*Total*
Normal refraction	108	2	110
Abnormal refraction	26	13	39
Total	134	15	149

χ^2 = 28·20. DF = 1. P = 0·000 011%

86% of squint/amblyopia in 26% of the population

(*b*) +2·50 or more D in any one (or more) meridian

	Normal vision	*Amblyopia*	*Total*
Normal refraction	124	3	127
Abnormal refraction	10	12	22
Total	134	15	149

χ^2 = 50·78. DF = 1. P = 0·000 000 05%

80% of squint/amblyopia in 14·9% of the population

(*c*) +3·00 or more D in any one (or more) meridian

	Normal vision	*Amblyopia*	*Total*
Normal refraction	129	7	136
Abnormal refraction	5	8	13
Total	134	15	149

χ^2 = 35·68. DF = 1. P = 0·000 000 22%

53% of squint/amblyopia in 8·7% of the population

It seemed logical to follow this by considering not only the refractions of individual eyes but the refraction in individual meridia of individual eyes. If one looks at this from the point of view of the level of hypermetropia in one or more meridia of a pair of eyes, an interesting association emerges (Table 8): 86% of those children who were eventually found to have squint/amblyopia were among 26% of the children screened who had +2·00 or more D in one (or more) meridia at age 1 year. 80% of those who had squint/amblyopia were among 14·9% of the children who had +2·50 or more D in one or more meridia at age 1, and a child who had +3·00 or more D in any one meridian had a slightly better than even chance of eventually having squint/amblyopia. Thus, meridional hypermetropia appears to be more significantly associated with the eventual identification of squint/amblyopia than bilateral hypermetropia and/or anisometropia or astigmatism. The lower level of meridional hypermetropia (+2·00 D) will detect the highest percentage of children who are destined to have a visual problem, but is the least selective. +3·00 D of meridional hypermetropia is the most selective but would 'miss' half of those children who eventually have a defect. In between, there is the extremely highly significant association (P=0·000 000 05%) between +2·50 D or more of hypermetropia in any one or more meridia at the age of 1 year and the eventual identification of squint and/or amblyopia. There can be very little doubt that Kramar's (1973) suggestion that we might be able to predict events on the basis of refraction was correct.

HYPERMETROPIA IN INDIVIDUAL MERIDIA

When two factors are associated at this level of significance (less than 1 in 10 million chance) it is possible that they are one and the same thing or that one could be the cause of the other. If meridional amblyopia really is caused by stimulus deprivation, the possibility arises that stimulus-deprivation amblyopia, due to hypermetropia in any one (or more) meridia of either or both eyes in infancy, is the basic factor common to the whole range of childhood squint/amblyopia problems as they present to us. It is interesting to speculate on what could follow from this.

MERIDIONAL HYPERMETROPIA, STIMULUS DEPRIVATION, AMBLYOPIA AND SQUINT

If you can have stimulus deprivation amblyopia in one meridian of each of a pair of eyes (meridional amblyopia explaining reduced acuity found with some bilateral hypermetropic astigmatic refractions), you can also have stimulus deprivation amblyopia in unilateral astigmatism (such an eye would be considered to be anisometropic) or in both the vertical and horizontal meridia of one and the same eye, with or without any combination of these in the fellow eye. If there is a period of life before which an eye can accommodate sufficiently to accurately focus light entering the eye(s) in all meridia (Haynes *et al.,* 1965), there would be stimulus deprivation in either or both meridia of one and/or both eyes according to the hypermetropia (in one or more meridia) above which the eye(s) was capable of accommodating. Ikeda and Tremain (1978) have recently shown that unilateral or bilateral atropinisation during the sensitive period resulted in unilateral or bilateral amblyopia in kittens. In addition, Blakemore and Eggers (in press) have demonstrated in kittens a loss of spatial resolution of cortical cells driven from one of a pair of eyes artificially made hypermetropic during the sensitive period.

The amount of hypermetropia might be the important factor, for example, the bilateral amblyopia which is recognised in association with high spherical hypermetropic refractions. However, it is also possible that an astigmatic eye does not, or cannot, automatically accommodate for the more hypermetropic meridian if the less hypermetropic meridian is easily focused. Thus, the stimulus deprivation might be related to the amount of hypermetropia in the more hypermetropic meridian or a combination of this and the difference in hypermetropia between the two meridia of one (or both) eyes.

As the eye(s) developed the ability to accommodate, and/or if the eye(s) became less hypermetropic (in one or more meridia), any 'deprivation' would progressively become less and the stimulus required to develop or maintain the neuronal connections would develop. Clear visual stimulus would, therefore, depend on how quickly an eye developed the ability to accommodate for all meridia relative to the rate at which any hypermetropia in any one or more meridia decreased. If this is related to the duration of the sensitive period, we could imagine stimulus-deprivation amblyopia as being the end result of a combination of circumstances occurring, and changing, during the first weeks or months of life. Thus, hypermetropia (in one or more meridia) might be the cause of the basic defect (primary amblyopia) not because it caused excessive or unusual accommodation and therefore squint, but for precisely the opposite reason, namely, before the eye could accommodate sufficiently, such an eye would present a blurred picture to the brain.

Furthermore, if there was some degree of stimulus-deprivation amblyopia, unilateral or bilateral, there could also be some defect of binocular vision (a microtropia?). Only later, when accommodation was possible and required in order to obtain clear vision (that is, if both eyes or if the master eye had a spherical hypermetropic refraction) would there be an unusually marked tendency for hypermetropia to result in accommodation, which in turn would lead to manifest esotropia. This would then be superimposed on a basic defect of binocular vision, and, if the esotropia was uniocular and prolonged, a further set of circumstances could operate and lead to what we have called 'secondary' amblyopia (Ingram *et al.,* 1977).

So far we have assumed that hypermetropia tends to decrease during the sensitive period, but there is no evidence for this yet, and an 'abnormal' amount of hypermetropia can increase after the age of 1 year (Ingram and Barr, 1979a). Moreover, an eye which originally had a normal refraction can occasionally become significantly hypermetropic in one or both meridia after the age of 1 year. We suggest that such an eye(s) originally presented no barrier to the normal development or maintenance of the cortical neurones, and therefore is not associated with amblyopia or any basic defect of binocular vision. If hypermetropia increased in one meridian of both of a pair of such eyes, we should have a child presenting with blurred vision and hypermetropic astigmatism. Correction of the refractive error would yield normal vision. Increase in hypermetropia in both meridia of both eyes would necessitate increased accommodation, and since accommodation is tied to convergence we could have, in the absence of previous stimulus deprivation, a child presenting with a wholly accommodative esotropia—one which would be *cured* by optical correction alone. Increase in hypermetropia in one or both meridia of only 1 eye could explain the 'straight-eyed anisometrope' who does not have any amblyopia. It would not be necessary to predict a child who would present under any one of the three above circumstances, since the 'defect' would be readily corrected optically. This would be in marked contrast to the need to identify abnormal hypermetropia present during the sensitive period, because such refractions might leave a permanent defect.

We do not claim that our hypothesis, based as it is on the relatively small number of children in this report, explains the enigma of squint/amblyopia. For example, it does not explain the essential alternator who presents before the age of 1 year, or the occasional accommodative esotropia of infancy (Pollard, 1976). Nevertheless, it could provide a new and different basis for further thought. If it was correct, then total cure would be possible only by correction of abnormal refractions during the sensitive period. If correction at a given age proved ineffective, then either the sensitive period had ended before the refraction was corrected, or, if it was ultimately found to be impossible to cure by this means, the cause of the visual defect must be something else, for example, a genetically determined absence of neurones.

We suggest, therefore, that investigation should proceed to: (1) identify the refraction that is most likely to lead to correct prediction of future visual defects, and therefore enable selection of children for trial of optical correction; (2) identify the age at which optical correction leads to a significant number of 'cures', and thus indicate when we are within the sensitive period in man.

We have started to do this, but think that the age of 1 year may be too late. We do not know of any reason why we should expect the duration of the sensitive period in man to be different from that of other mammals such as monkeys, and we recognise that the sensitive period may not end abruptly. Meanwhile, it would be helpful to know more about how refraction changes as children grow. Further, we need to know how effective cyclopentolate is as a cycloplegic and whether this is the drug of choice for this type of work.

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Uptake and loss of tears from filter paper discs employed in lysozyme tests

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SUMMARY Aspects of the use of filter paper discs in collecting tear samples for lysozyme tests were studied by serial weighings of bijoux bottles and tear-moistened discs. Blotted discs carried from 1·9 to 3·6 mg tears, but for practical purposes no deposit was left in the bottle. Unblotted discs carried a greater quantity of tear fluid, but the majority deposited a proportion of this in the bottle, and a correcting factor is therefore proposed for the lysozyme assay technique of Mackie and Seal. Substantial vaporisation of tears occurred within the bottles.

Filter paper discs may be employed as a means of collecting tear fluid for estimation of lysozyme activity. In the assay of tear lysozyme it is necessary that each tear sample be of constant quantity or that individual weights of samples are known. Van Bijsterveld (1969) collected tear samples by placing a 6-mm filter paper disc in the lower conjunctival fornix, allowing it to become entirely wet, and then blotting off excess fluid between a filter paper. In his results possible variation in tear content of the disc was not considered. Mackie and Seal (1976) collected tear samples in a similar way but without blotting the discs. The quantity of tears collected was determined by weighing a bijou bottle containing the 6-mm filter paper disc first dry and then after the disc had been soaked with tears. The filter paper was then removed from the bottle and transferred to an agar plate for lysozyme estimation. They found that the quantity of tears held by the unblotted disc could vary by up to fourfold, but, with the known weight of tears collected being taken into account, the lysozyme concentration was expressed in units of activity per microlitre of tears. Subsequently the method has also been employed in a slightly modified form, a 5-mm disc being placed in a 30×10 mm tube (Mackie *et al.*, 1977).

Two questions arise from the use of these techniques: firstly, whether it is correct to assume that blotting the discs will result in a constant weight of tears in each sample; secondly, whether discs, either blotted or unblotted, may leave behind a deposit of surplus tears in the bottle in which they are weighed. A trial was undertaken to answer these 2 questions and in addition to examine the possibility of vaporisation of tears within the bottles.

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Methods

Fifty normal volunteers (ages 17 to 59 years) agreed to take part in the trial, and two procedures were followed.

FIRST PROCEDURE

Empty bijoux bottles were weighed. A sterile Whatman No. 1 filter paper disc, 6 mm in diameter, was placed in the lower conjunctival fornix by means of forceps and allowed to remain until it was seen to be soaked. From 1 eye the disc was removed and placed directly into a bijou bottle, and allowed to rest on the side for 2 to 3 seconds. It was then withdrawn from the bottle and discarded, and the bottle tightly closed. From the second eye exactly the same technique was followed, except that, prior to placing the soaked disc in the bottle, it was allowed to rest on a Whatman No. 1 filter paper for a few seconds until it could be seen that all surplus tears had been absorbed. Within 2 hours, and usually within 1 hour, the bijoux bottles were reweighed to determine whether any tears had been deposited by contact with the discs.

SECOND PROCEDURE

This was undertaken on a separate occasion from the first procedure. Bijoux bottles were weighed, each containing a sterile 6-mm filter paper disc. The disc was taken from the bottle and placed in the

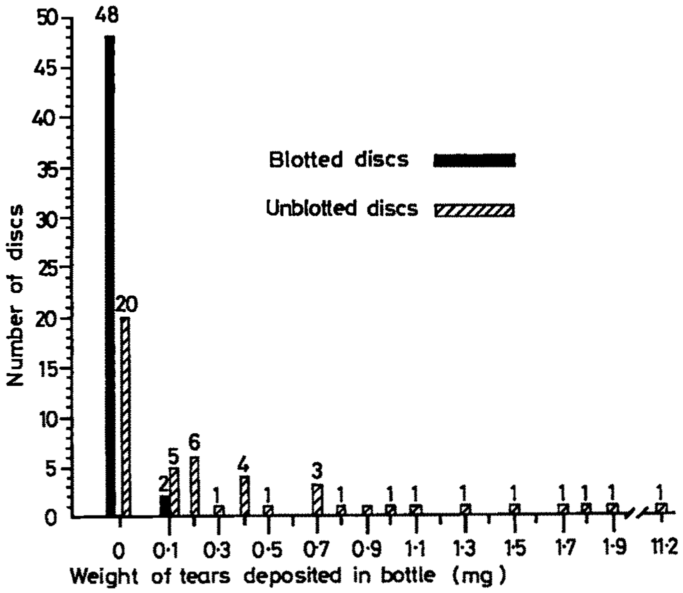

Fig. 1 *Tears deposited in bottle by contact with disc*

lower fornix and allowed to remain until soaked. From 1 eye this was then returned directly to the bottle, which was immediately closed. From the second eye the disc was blotted, as in the first procedure, and then returned to the bottle. Within 2 hours the bottles were weighed to determine the quantity of tears absorbed by the discs. Each disc was then removed from the bottle and weighed wet. Finally, after it had been allowed to dry out completely at room temperature the disc was again weighed.

Results

FIRST PROCEDURE

Tears deposited in bottle. Results of the first procedure are displayed in Fig. 1, where it can be seen that of the 50 blotted discs 48 left no measurable tear deposit in the bottle, while the remaining 2 each deposited 0·1 mg. Of the 50 unblotted discs 20 left no tear deposit, 29 left measurable weights up to 1·9 mg, and 1 disc deposited 11·2 mg. (A Kolmogorov-Smirnov 2-sample test (2-tailed) (Siegel, 1956) gave $P < 0{\cdot}001$, showing a highly significant difference between the blotted and unblotted samples.)

SECOND PROCEDURE

Tears absorbed by discs. Fig. 2 shows the blotted discs to hold 1·9 to 3·6 mg tears (mean 2·57 mg, SD 0·36). The unblotted discs can be seen to have absorbed from 2·2 to 8·9 mg, with one exceptional disc holding 15·1 mg tears (mean 5·25 mg, SD 2·13) (Kolmogorov-Smirnov 2-sample test (2-tailed) bebetween blotted and unblotted samples: $P < 0{\cdot}001$).

Tears remaining in discs on removal from bottle. These results are introduced in the discussion of loss of tears by vaporisation.

Discussion

BLOTTED DISCS

Fig. 1 shows that only 2 blotted discs deposited a measurable weight of tears on contact with the bijou bottle. In each case this was 0·1 mg, the smallest weight detectable by the balance, and its loss would not affect the lysozyme test. For practical purposes, therefore, it may be accepted that no tear deposit occurred from the blotted discs.

The tear weight in the blotted discs (Fig. 2) has been seen to be inconstant and to range from 1·9 to 3·6 mg about the mean 2·57 mg (SD 0·36). In the statistical analysis of his diameters of lysis van Bijsterveld (1969) obtained a variance of 0·2 (representing a change in zone of lysis of 0·45 mm = 1 SD) both within normal persons and between eyes within normal persons. He did not consider the possibility of variation in tear weight in the discs but interpreted the variance as an alteration in the individual. A lysozyme concentration/diameter of lysis curve is not given in van Bijsterveld's paper, which precludes a direct calculation of the variation in zone of lysis which would result from change in tear content in his filter paper discs. (Van Bijsterveld employed Whatman No. 3 filter paper. Per unit

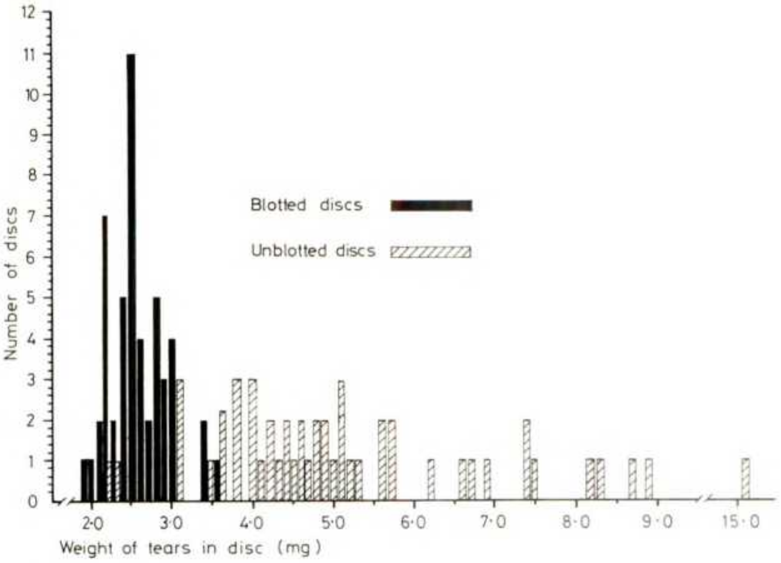

Fig. 2 *Weights of tears absorbed by discs*

weight of paper this absorbs 7% more fluid than Whatman No. 1, but the variation in uptake is closely comparable in the 2 papers.)

However, estimation of this variation is possible in the case of published curves. Two examples are presented in Table 1, giving the alteration in diameter of zone of lysis which would result from 14% change in tear weight in the disc (14% change ≡ 0·36 mg (1 SD) above or below mean tear weight 2·57 mg; estimation made on curve at mean lysozyme concentration in normal eyes). It is seen that the magnitude of zone variation is closely comparable with the figure of 0·45 mm found by van Bijsterveld. It is concluded, therefore, that variances of this degree found by van Bijsterveld could be attributed to alteration in tear volume in the discs rather than a presumed qualitative change in the tears of the individual. These findings do not, however, affect his conclusions on the reliability of his lysozyme test, the variances having already been taken into account in his analysis.

Table 1 *Changes in diameter of zone of lysis resulting from increasing and decreasing tear weight by 14% (equivalent to a change of 0·36 mg above and below mean 2·57 mg)*

Paper	*Increase in diameter*	*Decrease in diameter*
Bonavida and Sapse (1968, Fig. 1)	0·36 mm	0·41 mm
Pietsch and Pearlman (1973, Fig. 1)	0·55 mm	0·63 mm

UNBLOTTED DISCS

Substantial quantities of tears were deposited in bijoux bottles by many of the unblotted discs (Fig. 1). This deposit would be of whole tears, that is, containing lysozyme, the loss of which would affect the results of a lysozyme test. If it is assumed that the weight of tear deposit occurring from a disc is proportional to the quantity carried, the deposits (Fig. 1) can be related directly to the quantities in the discs (Fig. 2), disc for disc in order of tear weight. In Fig. 3 the fraction of tears lost from each disc by contact with the bottle, estimated in this manner, is plotted against the original weight of tears in the disc. It is seen that for discs carrying up to approximately 4·5 mg tears no loss occurs, but with larger quantities tears are deposited in increasing propotion, there being a remarkably close correlation between the two variables (correlation coefficient = 0·97, $P < 0{\cdot}001$).

Had the lysozyme assay technique of Mackie and Seal (1976) been performed on the tear samples in this trial there would have been an underestimation of lysozyme activity ranging from 2 to 22% in 29 cases, but in the exceptional tear sample of 15·1 mg the error would be likely to have exceeded 60%. In their paper Mackie and Seal (1976) report mean tear volumes collected of 5·1, 4·5, and 4·3 μl (largest volume 8·5 μl). This indicates that approximately 50% of their samples exceeded 4·5 mg in weight and will have left deposits in the bijoux bottles of up to a maximum 24% of tear weight. The estimations of lysozyme concentration will therefore be deficient in these cases, and the mean lysozyme

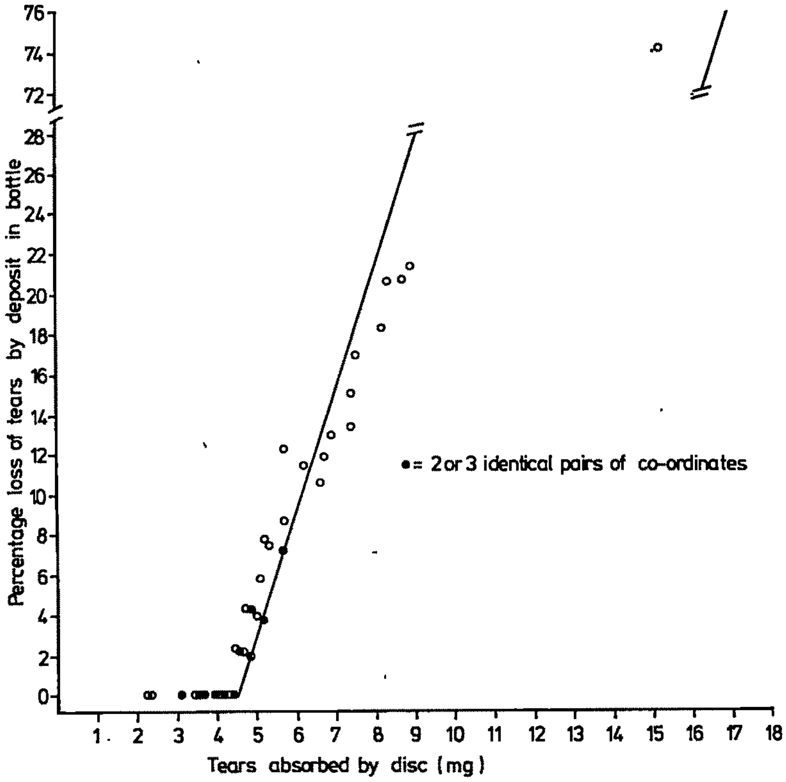

Fig. 3 *Proportion of tears deposited in bottle*

concentration line (Mackie and Seal, 1976, Fig. 3) will be lower than the true mean. It is also possible that the critical level is similarly incorrect. However, without knowledge of the weight of each individual tear sample the exact error cannot be determined.

It is possible to overcome this underestimation by applying a correcting factor to determine the tear weight remaining in the disc after any deposit has occurred in the bottle. For tear weights up to 4·5 mg, as measured by weighing the bottle containing the moistened disc, no correction is required. With weights exceeding 4·5 mg:

$$D = 1{\cdot}27\,b - 0{\cdot}061\,b^2$$

where D = weight of tears remaining in the disc after deposit has occurred, and b = original tear weight (bottle weighed containing moistened disc).

The above formula relates to 6-mm discs and may not necessarily be correct where glass bottles are replaced by plastic tubes. The alternative is to blot the discs and thus prevent loss of tears by contact with the container.

LOSS OF TEARS BY VAPORISATION

While deposit of tears in the bottle is loss of whole tears, resulting in error in lysozyme estimation, loss by evaporation will not alter the lysozyme content of the disc. It will, however, affect the weighing of tear samples.

The weight of tears remaining in each disc on removal from the bottle was determined from wet and dried disc weights. This figure was subtracted from the original weight of tears collected, the difference representing the weight of tears remaining in the bottle. In the case of the blotted discs this was due to vaporisation within the bottle, there being for practical purposes no contact deposit of whole tears. The tears left in the bottle by the unblotted discs were a combination of tear deposit and vapour, but by subtraction of the estimated deposit the figure for vaporisation was obtained.

It was found that moisture remaining in the bottle from vaporisation was: blotted discs 0 to 32% of tear weight (mean 14·6%); unblotted discs 0 to 36% of tear weight (mean 17·2%). In neither case was there a significant relationship between original tear weight and loss by vaporisation ($P > 0{\cdot}5$).

It is clear, therefore, that a substantial proportion of tears may vaporise inside the bottle, and in techniques where tear weight is taken into account it is important that the discs are weighed while still enclosed within the bottle, as, for example, in the method of Mackie and Seal (1976).

I am indebted to Dr A. Percival for technical advice, to Dr M. J. Coombs and Dr J. R. Green for statistical advice, and Mr R. Mapstone and Mr S. I. Davidson for support and encouragement.

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Isolation of *Chlamydia trachomatis* from eye secretion (tears)

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SUMMARY Shedding of *Chlamydia trachomatis* in the eye secretion (tears) of patients with either hyperendemic trachoma or paratrachoma was studied. The method of collection of eye secretion with cellulose sponges is proved to be simple, faster, and more practicable and yielded a higher rate of chlamydial isolation than aspiration. The chlamydial isolation rates in eye secretion in chlamydia-positive paratrachoma patients in London or trachoma patients in Iran was 84 and 49% respectively. It was found that the chlamydial isolation rate from eye secretion is directly related to the number of inclusions present in the conjunctival swabbings. The results of this study indicated that patients with moderate to severe hyperendemic trachoma or paratrachoma are the main reservoir of infection. In the developing countries of the Middle East and Africa the shedding of chlamydia in the eye secretion of persons with these diseases is a major factor in the transmission of them by means of flies, fingers, towels, or bed clothes.

Hyperendemic trachoma is commonly transmitted from eye to eye in circumstances which involve frequent contacts between eyes or the discharge therefrom (Jones *et al.*, 1976). Flies, fingers, towels bed-clothes, and other clothes are considered to have an important role in the transmission of hyperendemic trachoma. Recently Jones *et al.* (1976) demonstrated that flies can transmit fluorescein-labelled eye discharges from the eyes of one child to the eyes of adjacent children with remarkable speed and precision.

Paratrachoma of sexually transmitted origin (inclusion conjunctivitis, TRIC punctate kerato-conjunctivitis, and endemic trachoma), which is prevalent in the urban communities of developed countries, is commonly transmitted from the genital tract to the eye and only rarely by eye to eye transmission (Jones, 1964).

The present investigation was undertaken to provide quantitative data on the shedding of *Chlamydia trachomatis* in the eye secretion (tears) of patients with either hyperendemic trachoma or paratrachoma and to examine the correlation with the presence of viable chlamydia in the conjunctiva.

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Patients and methods

SELECTION OF PATIENTS

Patients included in this study were those attending the External Eye Disease Clinic, Moorfields Eye Hospital, London, with acute follicular conjunctivitis suggestive of paratrachoma, and the inhabitants of 3 villages in southern Iran with various grades of active trachomatous inflammatory changes or inactive hyperendemic trachoma.

COLLECTION OF EYE SECRETIONS AND CONJUNCTIVAL SWABBINGS

In all cases eye secretion was collected before conjunctival swabbings. In the first 28 consecutive London cases eye secretion from both eyes was collected by aspiration with glass capillary tubes, then were suspended in a plastic capsule containing 2SP transport medium (Gordon *et al.*, 1969) with additional 3% fetal calf serum, and stored in a liquid nitrogen refrigerator (–180°C). The amount of eye secretion collected from both eyes in this way was approximately 0·1 ml in each case.

In a further 20 London cases and in all patients in 3 villages in Iran eye secretion was collected by cellulose sponges (Spontex Ltd., Croydon, Surrey, England) measuring 5×3×1 mm. One sponge was placed in the lower fornix of the conjunctiva of each eye and allowed to become saturated with secretion. Sponges collected from the left and right eyes were placed together in one plastic capsule containing transport medium and stored in a liquid nitrogen refrigerator. The amount of eye secretion collected by sponges from the left and right eye together was approximately 0·1 ml.

After collection of eye secretion conjunctival swabbings were collected from the whole conjunctiva (upper tarsus, upper fornix, and lower lid) of the right and left eyes as described previously (Darougar and Jones, 1971). The paired swabbings from the right and left eyes were pooled in a plastic capsule containing transport medium and stored at –180°C.

ISOLATION TEST

The simplified one-passage technique of culture in irradiated McCoy cells (Darougar *et al.*, 1971) was used for isolation of chlamydia from eye secretion and conjunctival swabbings. Each specimen was inoculated into 2 tubes. Of these, 1 tube was fixed after approximately 60 hours' incubation, stained with Giemsa stain, and examined by dark-field illumination. The number of inclusions identified in this tube was recorded. The second tube was harvested and repassaged for serotyping of the isolates.

Results

In London the eye secretions from 28 consecutive patients were collected by aspiration and from a further 20 patients by cellulose sponges. In those patients with positive conjunctival swabbings the *Chlamydia trachomatis* isolation rate in eye secretions collected by aspiration or sponges was 75 and 100% respectively (Table 1).

Conjunctival swabbings and eye secretions were collected in parallel from a total of 752 patients in Iran. In these patients *C. trachomatis* was isolated in conjunctival swabbings in 57 (8%) and in eye secretion in 28 (4%) (Table 2).

In cases of paratrachoma the average numbers of inclusions obtained in conjunctival swabbings and in eye secretion were 436 and 75 respectively (Table 2). In 32 paratrachoma patients with positive conjunctival swabbings the eye secretion was negative in 5 (16%).

In 57 trachoma patients with positive conjunctival swabbings the eye secretion was negative in 32 (56%). In the trachoma group the eye secretion was positive in 3 patients whereas the conjunctival swabbings were negative. The average number of inclusions obtained in conjunctival swabbings and in eye secretions in these patients are shown in Table 2.

The isolation rate of *C. trachomatis* in eye secretion correlated well with the number of infectious chlamydial particles obtained from the conjunctiva by swabbings. In patients with over 1000 inclusions from culture of their conjunctival swabbings the eye secretion was positive in 75%, whereas in those with fewer than 10 inclusions from culture of their conjunctival swabbings this rate was only 31% (Table 3).

Table 1 *Isolation of* C. trachomatis *from eye secretion collected by aspiration or sponges and compared with isolation from conjunctival swabbings in patients with paratrachoma in London*

Method of collection	*No. of patients*	*No. of positive swabbings*	*No. of positive eye secretion*
Aspiration	28	20	15 (75%)
Sponges	20	12	12 (100%)

Table 2 *Isolation of* C. trachomatis *from eye secretion and conjunctival swabbings from patients with paratrachoma in London and hyperendemic trachoma in Iran*

		No. of positives		*Average No. of inclusions*	
Area	*No. of patients*	*Eye secretion*	*Conjunc. swab*	*Eye secretion*	*Conjunc. swab*
London	48	27 (56%)	32 (67%)	75	436
Iran	752	28 (4%)	57 (8%)	11	355

Table 3 *Chlamydial isolation rate in eye secretion in relation to the number of inclusions obtained from conjunctiva*

No. of patients	*No. of inclusions by swabbing (per patient)*	*No. of positive eye secretion*
12	Over 1000	9 (75%)
31	101–1000	19 (61%)
33	11–100	20 (61%)
13	1–10	4 (31%)

Discussion

In the present study the eye secretion was collected by aspiration in capillary tubes in the first 28 cases of paratrachoma. We found this method to be tedious, time-consuming, and hardly practicable. Alternatively, we used cellulose sponges for collection of eye secretion. This method is being used successfully in our laboratory and field work for detection of antichlamydial antibody in eye secretion (Treharne *et al.*, 1977; Darougar *et al.*, 1978). This method proved to be simple, faster, and more practicable for collection of eye secretion and yielded a higher rate of chlamydial isolation than did aspiration.

The chlamydial isolation rate in eye secretion in patients with positive culture (by swabbing) for *C. trachomatis* in London and in Iran was 27 out of 32 (84%) and 28 out of 57 (49%) respectively. This difference may be related to the degree of intensity of inflammatory changes in the conjunctiva and the number of inclusions present in the conjunctiva or the amount of eye discharge.

Darougar *et al.* (1977) have shown that the chlamydial isolation rate from conjunctiva is generally related to the intensity of inflammatory changes in the eye. In London and in Tunisia in patients with clinically diagnosed moderate to severe paratrachoma or trachoma the isolation rate for *C. trachomatis* was 90 and 73% respectively, whereas in patients with mild trachoma this rate was as low as 23% (Darougar *et al.*, 1977).

In the present study we found that the chlamydial isolation rate from eye secretion is directly related to the number of inclusions present in the conjunctiva as demonstrated by isolation tests from conjunctival swabbings. In patients with an average number of 1000 inclusions or more from their conjunctival swabbings the isolation rate in eye secretion was as high as 75%, but in those patients with an average number of 1 to 10 inclusions the eye secretion was positive in only 31% (Table 3).

The result of this study indicates that patients with moderate to severe hyperendemic trachoma or paratrachoma are the main reservoir of infectious agent being shed from the eyes. They are harbouring more infectious agent and are shedding greater numbers of viable particles in their eye secretion. It is also possible that the excess amount of mucoid discharge in the eye of these patients may have an important role in protecting chlamydia from adverse effects of environmental factors.

In the developing countries of the Middle East and Africa the shedding of chlamydia in eye secretion of patients with moderate to severe trachoma is a major factor in transmission of the disease by means of flies, fingers, towels, or bedclothes. In London, although shedding of chlamydia in eye secretion is common, the eye to eye transmission of the disease is rare (Jones, 1964). This, in general, is due to higher standards of personal and ocular hygiene and the absence of eye-seeking flies in the community.

In eye secretion antichlamydial antibody has been found in 85% of patients with paratrachoma (Darougar *et al.*, 1978), and in up to 47% of patients with moderate to severe hyperendemic trachoma (Treharne *et al.*, in preparation). Barenfanger and MacDonald (1974) have shown that eye secretions with antitrachoma antibody neutralise the trachoma agent. However, isolation of chlamydia in eye secretion may suggest that in the patients' eyes antichlamydial antibodies may have little or no effect on chlamydia.

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Herpetic canalicular obstruction

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SUMMARY Viral infection is a common cause of acquired obstruction of the lacrimal canalicular system. A series of 20 patients with canalicular obstruction attributable to infection with herpes simplex is reported, and 1 case is described in detail.

The purpose of this paper is to describe the pattern of disease in the lacrimal drainage system resulting from infection with herpes simplex virus and to discuss the approach to investigation and treatment. A large proportion of canalicular blocks are attributable to viral infections of the external eye, and herpex simplex virus is an important pathogen in this regard. In recent years we have treated 20 patients in whom we are confident the cause of the acquired canalicular obstruction was herpes simplex virus. Here we review these cases as a group and report 1 typical case in detail.

Materials and methods

Twenty patients presented with evidence of herpetic disease and epiphora. Seventeen were female, 3 were male, and all were in the first 3 decades of life when they initially developed epiphora. The earliest onset of epiphora was at age 3 months and the latest at 26 years (Table 1).

In all cases the onset of epiphora was related to an episode of unilateral conjunctivitis associated with lid vesicles, although in some cases years passed before advice was sought. Five patients presented during this initial episode, and a diagnosis of primary herpes simplex blepharokeratoconjunctivitis was made. In others the primary attack had long subsided before the patient realised the epiphora was to be a permanent sequel to the initial infection.

Eleven patients developed recurrent dendritic ulceration, and 4 others had corneal scarring consistent with healed herpetic keratitis, although they denied symptoms. In 3 cases positive isolates of herpes simplex virus were obtained, although no active herpetic process was apparent. The pattern of herpetic disease in the external eye is set out in Table 2.

Table 1 *Distribution of the ages of 20 patients presenting with epiphora attributable to infection with herpes simplex virus*

0–	*5–*	*10–*	*15–*	*20–*	*25–29*
3	8	3	5	0	1

Table 2 *Manifestations of herpetic disease in 20 patients with canalicular obstruction attributable to herpes simplex infection*

Manifestation of herpetic disease	*No. of patients*
Primary blepharokeratoconjunctivitis	20
Recurrent dendritic ulceration	11
Corneal scarring without symptoms	4
Herpes simplex virus isolated	3

The site of the canalicular pathology was remarkably consistent, the midzone being affected in all cases and the proximal end of the block being 2 to 6 mm beyond the puncta, which were invariably normal. The upper and lower canaliculi were affected in each case. Only 9 of the 20 cases had been treated with 5-iodo-2′-deoxyuridine (IDU) prior to the development of epiphora.

Biopsy material was obtained from 3 cases at the time of bypass surgery. Light microscopy showed areas of fibrosis with mononuclear cell infiltration, and with electron microscopy particles which could represent herpes simplex virus were seen (Fig. 1). The size of the particles is consistent with their being herpes simplex virus, as is the shape—round with a light core and dark outer zone.

Treatment

Midcanalicular disease is not amenable to plastic reconstructive surgery, and in all cases it eventually proved necessary to perform a bypass procedure

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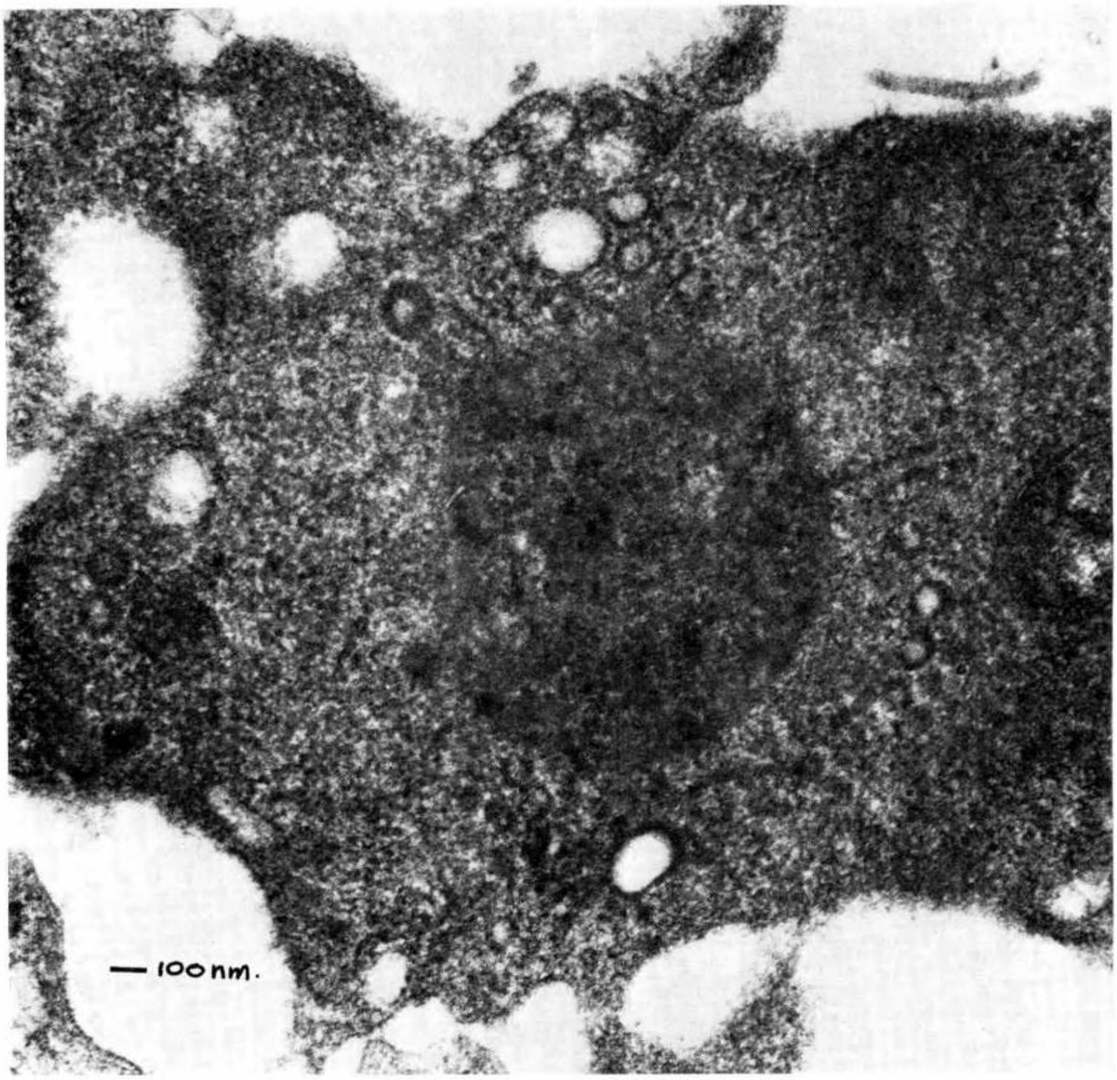

Fig. 1 *Electronmicrograph of excised area of occluded lacrimal canaliculus. The round structures with a dense periphery have a size and morphology consistent with herpes simplex virus*

with a Lester Jones tube to cure the epiphora. The longest follow-up period was 7 years.

Case report

A 35-year-old man presented with epiphora which he had had for 10 years. The onset of symptoms coincided with a 2-week episode of unilateral conjunctivitis associated with lid vesicles. He had subsequently suffered several episodes of dendritic ulceration of the cornea.

The lacrimal puncta appeared normal, the sac was not palpable, and syringing revealed a patent upper canaliculus, but the lower canaliculus was obstructed 3 mm beyond the punctum. The conjunctiva was normal, but the cornea was scarred centrally. Intubation macrodacryocystography confirmed the blocked lower canaliculus and a patent upper canaliculus, which was irregular in the midzone (Fig. 2).

To identify herpes simplex virus positively as the cause of the disease is more difficult. Virus isolation studies were negative, complement fixing antibodies were demonstrated at a 1:20 titre, but herpes simplex

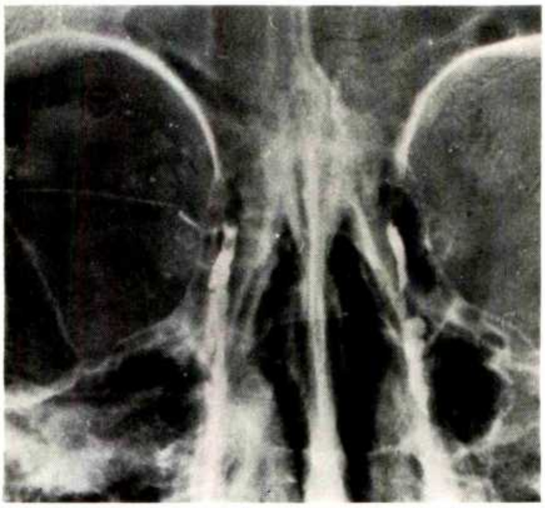

Fig. 2 *Intubation macrodacryocystogram showing occluded lower canaliculus and irregular lumen of midzone of the upper canaliculus*

virus antibodies are found in 75% of the community (Andrewes and Carmichael, 1930). This level is indicative of exposure to antigen at some point and is consistent with a primary infection 10 years previously.

Initially an attempt was made to perform a canaliculostomy, but this failed to control the epiphora. Because only the lower canaliculus was obstructed and the upper canaliculus was apparently patent, a dacryocystorhinostomy was performed. This procedure is often successful when only 1 canaliculus is patent (Jones and Corrigan, 1969). However, in this case the epiphora persisted, presumably because the upper canaliculus, although patent, is quite irregular and unable to function normally. Only when a Lester Jones tube was inserted did the patient become symptom-free.

Discussion

Viral infections are a well-recognised cause of acquired canalicular obstruction (Bouzas, 1965; Sandford-Smith, 1970; Wise, 1976; Welham, in press). They constitute the second most common cause of acquired canalicular obstruction in our practice. A breakdown of the causes of canalicular obstruction treated surgically over a 10-year period to 1976 is set out in Table 3. Other viral diseases are known to cause canalicular obstruction, but in patients treated in the Lacrimal Clinic at Moorfields Eye Hospital, City Road, London, herpes simplex virus was the most common.

The diagnosis of herpetic canalicular obstruction in the 20 cases reported here was based on clinical findings and laboratory investigations. The major obstacle to confirming the clinical diagnosis with virus isolations is the long period between the occurrence of the active disease process and the presentation with epiphora. Almost always the disease is quiescent by the time the patient realises the watering is a permanent sequel to the inflammation of the external eye.

The importance of the primary infection with herpes simplex virus is emphasised by the fact that all patients dated their symptoms from an episode of vesicular blepharokeratoconjunctivitis and the youth of those afflicted. The remarkable similarity in the clinical features exhibited in this group may be due to our preparedness to recognise these more obvious cases. No cause is apparent in most cases of nontraumatic acquired canalicular obstruction. Perhaps within this group infective causes are important but are less obvious in their manifestations. That both canaliculi are affected in all 20 cases suggests that we are looking at the more severe end of the spectrum, and other patients with herpetic infections of the external eye may have their canaliculi affected but not extensively enough to result in epiphora.

Antivirals are known to cause obstruction of the lacrimal drainage system, but the clinical picture is different. Idoxuridine was the first to be seen to affect the drainage system, and more recently trifluorothymidine (F_3T) and adenine arabinoside (Ara-A) have been implicated. Such a complication of therapy is unusual, and it is the punctum that is seen to be occluded rather than the midzone of the canalicular system. Unlike the obstruction caused by herpes simplex virus, the punctal changes occurring with antiviral toxicity reverse on withdrawal of the drug.

The presence of midcanalicular occlusion is best established by passing lacrimal probes; macrodacryocystography is seldom satisfactory because of the difficulty encountered in achieving intubation. Usually the young patients affected with herpetic

Table 3 *Causes of epiphora treated by canalicular surgery (1968–76)*

Viral canaliculitis	26
Trauma	21
Congenital	15
Iatrogenic	11
Streptrothrix	2
Stevens-Johnson syndrome	1
Unknown	54

canalicular obstruction have severe watering, and surgery is often necessary. Failure to appreciate the nature of the postviral infection block can be compounded by inadequate surgery, the lateral extent of the lesion being overlooked. Dacryocystorhinostomy always fails in this situation.

Bypass surgery is necessary and a very successful treatment for this form of lacrimal drainage obstruction. The disadvantages of Lester Jones tubes are made light of by the young, highly motivated patients affected with postherpetic canalicular obstruction.

The histological material was prepared in the Department of Pathology, Institute of Ophthalmology, London.

Professor Alec Garner provided invaluable advice on the interpretation of the pathology.

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An aid to successful probing of the nasolacrimal duct

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SUMMARY An electrical method is described for confirming the entry into the nose of a nasolacrimal probe.

The average ophthalmic surgeon is unlikely to flatter himself about his ability to visualise the lower end of the nasolacrimal duct, particularly in those patients, small infants, in whom an obstruction at this site may be of clinical importance. It has furthermore been suggested that the probing of the nasolacrimal duct in such patients may fail if the probe pushes a fold of mucosa ahead of it instead of perforating it.

Materials and methods

At the suggestion of my otorhinolaryngological colleague, Mr John Groves, I have found that true patency can be confirmed electrically. The probing is carried out under general anaesthesia by one of the standard methods. The lower canaliculus is probed first to investigate and ensure patency into the sac. The nasolacrimal duct is then probed via the upper canaliculus. With the No. 0 probe in position an electrode is clipped on to it which connects with a battery-activated light (Fig. 1). The other terminal from this is attached to a No. 1 lacrimal probe, which is then used to explore the inferior meatus of the nose. If and when it comes in contact with the end of the probe emerging from the nasolacrimal duct, the circuit is closed and the bulb lights.

The electrical circuit is easily constructed; it incorporates a 6 V battery and 2·7 W bulb.

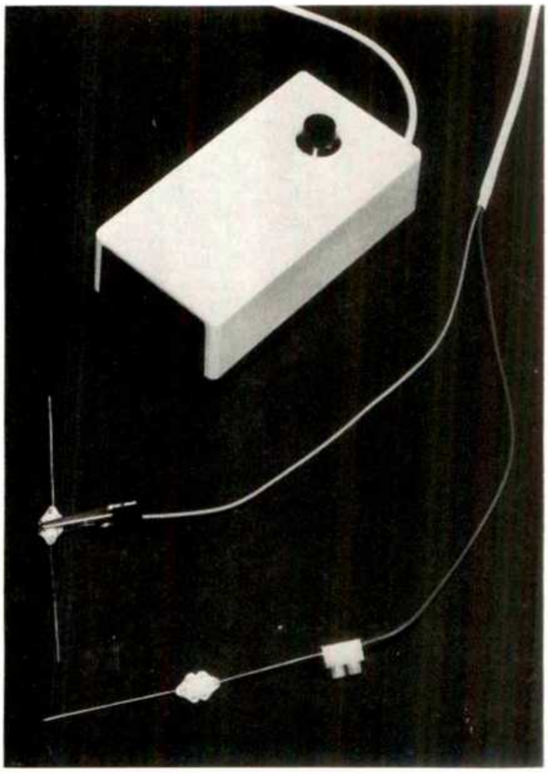

Fig. 1 *Equipment for probing nasolacrimal duct*

Discussion

Some points of note are as follows. Firstly, the nasal probe has to be directed not only backwards but slightly outwards and even downwards to get under the inferior concha. Secondly, the time taken to establish electrical contact may help haemostasis in any area of the duct where the passage of the probe has led to rupture of small vessels.

It is possible to make a rough estimate of the distance from upper punctum to the lower end of the duct. The probe is withdrawn up the nasolacrimal duct once electrical contact has been obtained until the light goes out. At the age of 12 months the distance is about 22 to 23 mm.

Patency confirmed electrically at least partially avoids any indication to syringe lacrimal passages, a procedure for which a cautious anaesthetist would prefer to intubate the patient. Intubation is therefore unnecessary when this test is employed.

The inexperienced young surgeon may be un-

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certain how far to push the probe down the duct. He may be unaware of passing through any obstruction or there may indeed be none. This device makes it easier for him to determine objectively that he has got into the nasal cavity when, not having felt any resistance, he thinks he has gone down far enough.

Making and breaking the circuit not only activates the light, it may also cause a twitch of the orbicularis. There are, one supposes, simpler methods of electrical stimulation of the orbicularis, and here it raises the possibility of some therapeutic use as in the problem of residual watering in an all but completely recovered Bell's palsy.

My thanks are due to the workshops of the Neasden and Royal Free Hospitals and to the Photographic Department of the latter.

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Keratoplasty sensitivity

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SUMMARY Analysis of graft sensitivity showed a return to normal after 3 years in only one-third of the eyes. It is not known whether this is due to regeneration of abnormal or superficial nerve fibres. Contact lens wearers showed less sensitivity than spectacle wearers.

The nerve supply to the cornea, while not being fully understood, has been described in detail in primates and particularly in man (Zander and Weddell, 1951). In contrast to other tissues the nerves function in only one modality, and that is pain. While temperature has been suggested as another sensation, it is not known whether specialised reactions follow such stimulus as compared with pressure in the area producing a sensation of pain.

The nerves in the human cornea have been described as emerging from the corneoscleral junction at various levels, but mostly deep, and then finally ending in the epithelial layer, becoming intimately associated with the deeper epithelial cells. Some fibres are medullated, but some are not. According to Lim (1978), using the monkey as an experimental animal, another system of sensory fibres exists on the corneal surface and originates from the plexus of nerves present in the conjunctiva. This other sensory supply has not so far been shown to exist in man. Also according to Lim, regeneration of corneal nerves occurs after section even at mid-brain level (Lim, 1978).

This study involves the recording of sensory levels in the human keratonus cornea that has had graft surgery. Two areas are taken at the periphery (host) and at the centre of the graft. In normal cornea the central zone is about 2 to 3 times as sensitive as the periphery (Millodot and Larsen, 1969). But age, individual apprehension, and even time of the day or month in women will cause some significant change in the degree of sensation (Millodot and Lamont, 1974).

Contact lens wear itself will markedly decrease sensation, especially with hard lenses (Boberg-Ans, 1956), but according to Millodot (1971) some sensation returns after several months of contact lens wear, the loss of sensation being over zones of corneo-contact lens pressure.

While the keratoconus eye does not have a normal cornea, there is nothing in the literature to suggest abnormal sensation except with obvious complications affecting the nerve supply. Some keratoconic corneas are hypersensitive and cannot tolerate contact lens wear. This may initiate the itching or subnormal pain sensation that results in eye rubbing. The very advanced cone may become severely scarred and then show loss of sensation at the apex.

The group of patients examined were randomly selected, and most had clear successful grafts. The periods from surgery to examination were 7 months to 10 years. Over 50 such eyes were examined with the Bonnet and Cochet regular aesthesiometer of Cochet and Bonnet (1960). This instrument has been used by several workers, and the defects and significant baselines for normal and abnormal response are well documented (Bonnet and Millodot, 1966; Millodot, 1969).

Analysis of the results will help to determine whether graft sensation is present and to what degree, how contact lens wear affects sensation, and also if the peripheral grafted recipient cornea has normal sensation.

Methods

The patient was asked to remove the contact lens, if worn, the night before examination, and the aesthesiometer was used as directed by the manufacturer's instruction. Beginning with a 'No' response, the nylon thread was decreased in length until a positive response was given, and the length of nylon was noted.

If doubtful responses resulted, the test was repeated at another visit. The patient was seated at the slit lamp and the positioning of the probe visualised under magnification. The eye was stabilised by using the other eye to fixate a light.

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In this test we assumed no clinical significance unless the variation was at least 1 mm alteration in nylon length (see 'discussion').

Results

Forty-eight grafted eyes were measured. The central graft readings recorded zero sensation in 7 and normal in 14 eyes (above 4 is normal), that is, no sensation 14·6%, subnormal 56·25%, normal 29·2%.

The mean average for centre of graft sensation was 1·8 mm. The peripheral sensation was 4 or over in 8 eyes, and in 1 patient the lowest reading was 0·5, the mean average for the peripheral cornea being 2·66 mm.

Table 1 analyses the average sensation according to the age of the graft from time of operation to taking of measurement.

No instance of normal central sensation was recorded until at least 3 years after surgery. Even at 6 years and over at least a third of the grafts measured could be said to be clinically anaesthetic, and one-third had normal sensation (Fig. 1).

The 27 contact lens wearing eyes had an average sensory response of 1·15, with 2 having normal sensitivity, and the 21 spectacle wearers had an average of 1·97 mm sensitivity, with 4 having normal sensitivity.

Conclusions

The graft has abnormal sensitivity beginning with zero readings after surgery, and sensation can be recorded in the first year but does not reach normal sensitivity until at least 3 years from time of operation, while contact lenses can be fitted from the sixth week or later and may therefore decrease any sensitivity present. Certainly contact lens tolerance is easier for the grafted eye than the normal. It was found that the sensitivity of contact lens wear in grafted eyes was 1·15 average as compared with 1·97 in non-contact-lens wearing grafted eyes (Fig. 2). But these figures may not be of significance in a clinical sense. Furthermore, a greater proportion of the spectacle wearers were found to be patients with grafts older than 3 years and preferred spectacle wear to contact lens wear even though the latter gave better acuity.

Table 1 *Average sensation according to age of graft from operation to measurement*

Age in years	*Average sensation*
Under 1	0·5
1—	1·1
2—	1·1
3—	3·0
4—	1·7
5—	1·8
6—	2·0
7—	2·50
8+	1·9

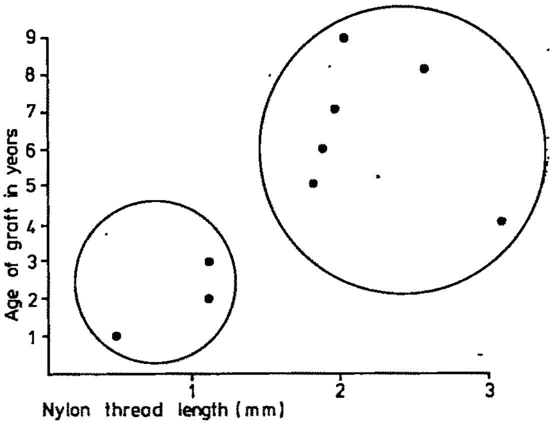

Fig. 1 *Average aesthesiometer results at graft centre*

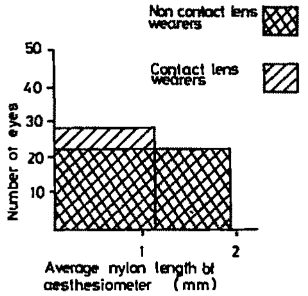

Fig. 2 *Graft eyes, contact lens wearers and nonwearers. Comparison of graft sensation*

The peripheral graft sensation was within normal, and it must be assumed that, since the average central corneal sensation is half normal, regeneration of nerves from the host into the graft is rarely more than 50% effective. Normal sensation in a graft was not found in more than one-third of the eyes examined. The return of sensation was progressive but relatively static 3 to 4 years after surgery.

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Keratoconus keratoplasty curvatures and contact lens wear

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SUMMARY Fifty-three grafted keratoconus corneas chosen at random from several hundred operated upon over a 10-year period showed an increase in myopia after removal of sutures but a decrease in astigmatism. With the photoelectrokeratograph machine the spherical zone was shown to be limited to 3 mm with gross eccentricities. Half the patients chose to wear contact lenses after surgery and 10% had no correction. Contact lens wearers showed a much greater decrease in astigmatism than spectacle wearers.

The treatment of keratoconus by keratoplasty would be ideal if the curvatures of the donor graft resulted in an emmetropic eye. But for several reasons this is rarely possible. The chief reasons given are light transmission defects of the graft tissue or irregularities in curvature of the donor corneal surface. Analysis of curvatures even suggested to previous workers that keratoconus recurs in the grafted eye. It will not be the purpose of this paper to discuss light transmission problems, which are chiefly concerned with endothelial survival and function, or the several problems that result in opacities, either partial or total, of the graft. The latter are usually associated with either inflammatory reactions of healing or immunological reactions.

The various aspects of graft size, shape, and suturing techniques have been dealt with by several workers. The conclusions so far are that, while size and shape may alter the final curvature (Ruben, 1972; Troutman and Meltzer, 1972; Troutman, 1973), the reasons why they do so are not fully known. According to Ruben (1972) the relationship between average keratometry and size was related to graft size; thus the large grafts resulted in overall flatter curvatures. Recent work by Davies *et al.* (1976) disputes a statistical relationship between number of sutures but favours more the tension present in sutures. Indeed, it is well known that the tension, when released on removal of sutures even one-and-a-half years after grafting, results in sudden changes of graft curvatures. This has led some surgeons to leave graft sutures of 10–0 Perlon in the eye indefinitely, provided vision is satisfactory and the astigmatism is low.

An alternative approach has been to mould the graft by means of a contact lens fitted some 6 to 12 weeks after surgery and with the Perlon sutures *in situ*, the contact lens usually being hard, but softer materials are often used.

This paper analyses the keratoplasty curvatures of 48 patients, of whom 5 had bilateral keratoplasty. The keratometry findings will be correlated with the age of the graft, and in those cases in which contact lenses have been worn the degree of initial astigmatism, with that after prolonged periods of wear, will be described. Mean average of graft keratometry and acuity will also be given. The value, therefore, of the contact lens as an adjunct to keratoplasty will be discussed from these results.

Further work on graft sensitivities and thickness has been done where possible in all these patients and will be reported in separate papers.

Method

The Contact Lens Department at Moorfields Eye Hospital has over a 10-year period done several hundred grafts routinely, chiefly of 7 or 8 mm diameter, by the conventional surgical technique of interrupted and more recently (over the past 6 years) of continuous-only suturing. Case reports have been taken from the files at random and the patients followed up as they attended the clinics, when they underwent careful testing of refraction, keratometry (including photoelectrokeratogram), and contact lens acuity.

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Results

AGE OF GRAFT

The shortest time from operation was 7 months and the longest time 120 months (10 years). The average for the group was 62·16 months (5 years).

The numbers in each graft age group were as follows: 0 to 12 months, 8; 1 to 2 years, 7; 2 to 3 years, 4; 3 to 4 years, 5; 4 to 5 years, 3; 5 to 6 years, 5; 6 to 7 years, 8; 7 to 8 years, 8; 8 to 9 years, 3; 9 to 10 years, 1; over 10 years, 1. Total, 53 grafted eyes.

Directly after sutures were removed (average, 6 months) the average spherical ametropia was –1·82 dioptres and the average astigmatism 4·12 dioptres; axis oblique in 75%; axis with the rule 15%; axis against the rule 10%. But at just over 5 years the refraction results were as follows: –3·64 for equivalent spherical ametropia, and average astigmatism 3·43 dioptres. The axes were oblique 74%; with the rule 13%; and against the rule 13%. There were 3 eyes in the last group without measurable astigmatism (below 0·25 dioptres), whereas all eyes before the sutures were removed had measurable astigmatism.

In 6 instances the astigmatism changed its axis more than 45°. Two cases showed a 90° change of axis; they were both contact lens wearers and the grafts were more than 3 years old. Where measurable, the corrected spectacle acuity immediately after sutures were removed averaged 6/12. But 11 patients had no measurable spectacle acuity at this time, possibly owing to graft irregularity and/or oedema. The final average acuity with spectacles was 6/13·7. The change of acuity could be analysed further in each graft age group, but the small numbers involved would not yield a statistically significant result. It was found that 67·5% had 6/9 or better acuity immediately after taking out the sutures, and at the 5-year average age period this figure had dropped to 58·7%.

The results are shown in Table 1.

Table 1 *Distribution of astigmatism after removal of sutures*

	After removal of sutures	*4 years average age of graft*
Average spherical equivalent ametropia	–1·82	–3·64
Astigmatism in dioptres	4·12	3·33
Axis of astigmatism, oblique	75%	74%
	15%	13%
	10%	13%
Acuity (average)	6/12·0	6/13·7

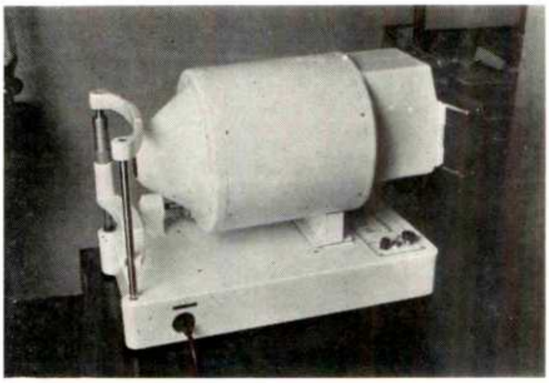

Fig. 1 *PEK Wesley-Jessen machine for topographical keratometry*

The highest degree of astigmatism measured was 13 dioptres in an eye immediately after removal of sutures.

A topographical photoelectrokeratograph (PEK) was done on the Wesley-Jessen machine (Fig. 1) in 20 patients and analysed to give eccentricity readings. The eyes were measured at the average time of 5 years.

Keratography shows alterations in the surface of the cornea by means of a photograph of the reflected image of a target. The target in the case of the photoelectric keratoscope is a series of illuminated concentric circles with the inner circles furthest away from the eye being photographed and the largest circle nearest. They are arranged in this manner so that their image in the cornea is flat. The camera is fixed so that its lens is concentric with the target.

To take a keratograph the patient's head is positioned in the headrest so that the eye to be photographed is aligned with the central target aperture. The patient focuses on the centre of the illuminated crosswire, which marks the centre. The operator views the reflected image through the eyepiece, which has a split screen to aid focusing. When the rings are continuous and in sharp focus the photograph is taken.

The keratograph must have at least three central rings in sharp focus in one meridian before the computer can evaluate the shape factor and eccentricity of the cornea photographed.

PEK ANALYSIS

The individual curves taken from PEK of grafted eyes selected at random have had their variances from the normal magnified × 1000 to show how graft curves differ quantitatively and qualitatively (Figs. 2 to 5). It must be pointed out that these individuals (denoted by numbers) have clear success-

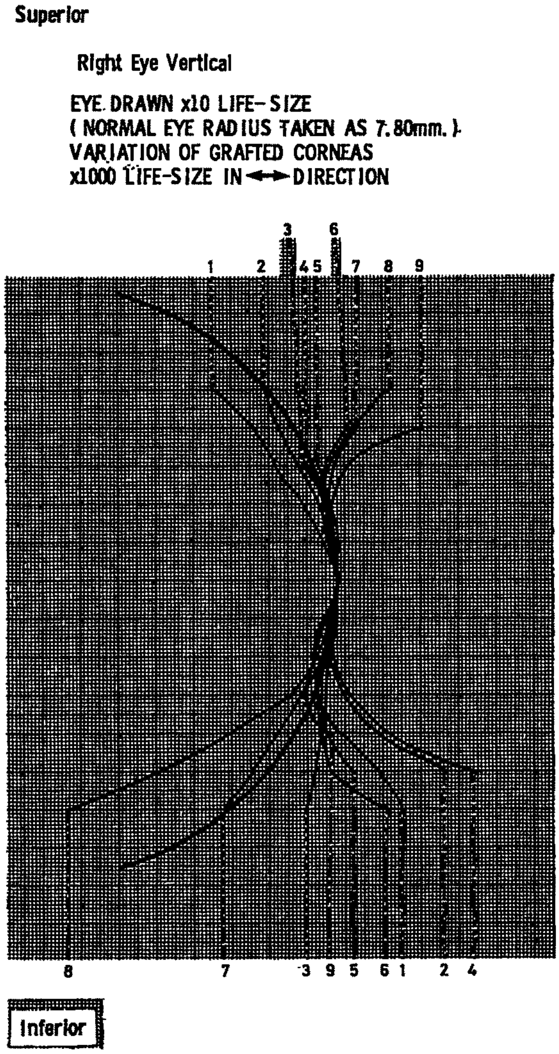

Fig. 2 *Vertical section, right eye, of 9 graft curvatures. Continuous black line = normal cornea; r = 7·8. PEK data × 1008 co-ordinate*

ful grafts and were corrected with contact lenses to the good acuities previously described.

The PEK measures the topographical keratometry in 2 meridians at 90° to each other over 10-mm chords. The diagram shows that the variance from normal corneal curve of $r = 7{\cdot}80$ over the central 1-mm chord is ±0·003 mm (measured in the line of the central axis); that at the limits of the 4-mm central chord the variance is ±0·009 mm; and that at 6 mm, which must be considered the limits of good optical quality of most grafts, the variance from normal is in the region of ±0·015 mm.

The graft outlines shown in this way give an impression that the majority of curves are within normal sphericity over a 3- to 4-mm chord, but then deviate. There are too few curves from which to draw statistically significant conclusions. But any corneal curve which progressively changes so that a difference of 1 dioptre occurs within a chord increase of 2 mm can be said to be clinically eccentric. With the above method of monitoring curves this is equivalent to a 0·10-mm deviation or ±0·05-mm variance. We see, therefore, on applying

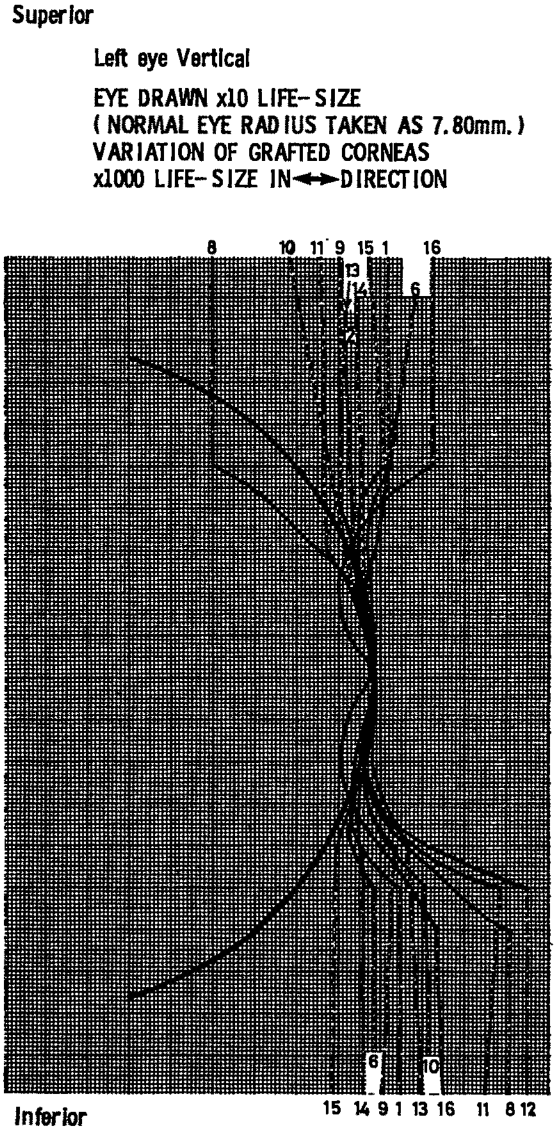

Fig. 3 *Vertical section, left eye, graft curvatures*

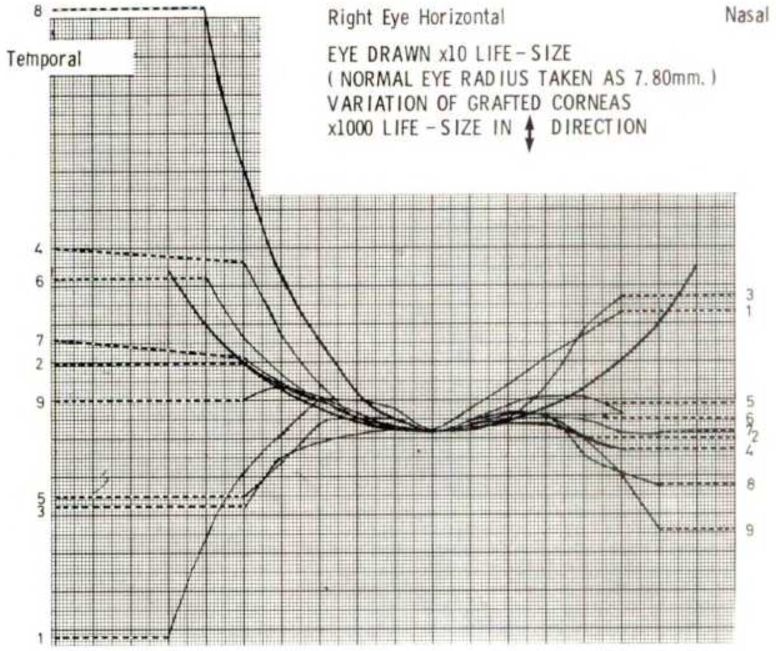

Fig. 4 *Horizontal section, right eye, graft curvatures*

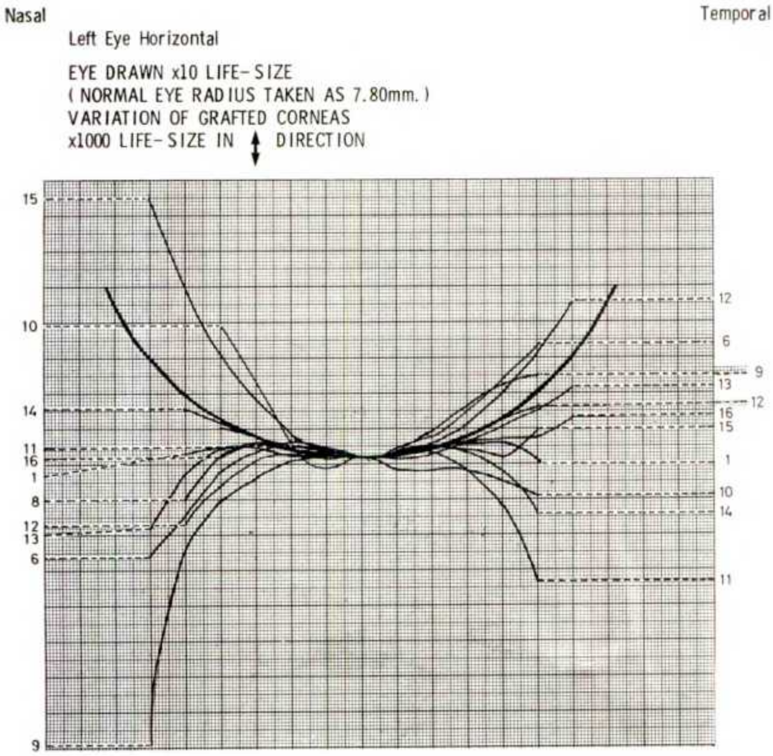

Fig. 5 *Horizontal section, left eye, graft curvatures*

this rough guide of clinically significant eccentricity, that with the exception of patients CN and GN, all eyes are better than this. However, the distribution of eccentricity is not regular in any meridian measured.

To correlate eccentricity of graft curvatures with acuity is difficult. It best relates to corrected spectacle acuity, and those patients obtaining 6/6 or better are 34·8% of the whole group. For such good acuities not only must the deviations from the normal be low but they must be the same in opposite meridians. For example, CJD (Figs. 2–5) is an extreme example of how the temporal and nasal deviations differ in the horizontal and in the vertical. Such eccentricities must be regularly placed about the centre in all quadrants to produce good acuity. Most of the curves illustrate this type of irregularity.

KERATOMETRY

The average keratometry after removal of sutures was 7·63, the average flattest readings being 8·09, and the steepest 7·18. The average astigmatism was 0·91 mm radius of curvature (5·0 dioptres); the steepest readings being 5·70 and the flattest 10·38 (not in the same cornea).

The readings taken at average age of graft 5 years after operation were respectively 7·42 (average), 7·75 (flattest), 7·11 (steepest), and astigmatism 0·4 mm (3·50 D), the steepest readings taken being 5·70 and the flattest 9·00 (see Table 2). There is therefore a significant change in K readings as the graft ages.

ANALYSIS OF ASTIGMATISM IN GRAFT AGE GROUPS

This was done to establish a trend, and the results are as follows. Table 3 shows that the 7- to 8-year-old grafts had a higher average astigmatism than the remainder. But since this result was due entirely to 3 high results (over 7 dioptres) out of a total of 7 cases it may have less significance.

No complete trend over the whole range could be seen, and high astigmatism after removal of sutures. But analysis of grafts where astigmatism was 4 dioptres or more after removal of sutures showed the following changes: 18 eyes with 4 D or more astigmatism had an average keratometry of 6·84 after sutures were removed. After 1 or more years the average was reduced to 3·58 D. There is a marked trend for the higher degrees of astigmatism to reduce, which is not shown so clearly with overall averages. However, comparison of similar groups does show the trend for grafts to decrease astigmatism as the graft ages.

Table 2 *Distribution of keratometry readings after removal of sutures*

	After removal of sutures	*At age of graft 5 years*
Average K	7·63	7·42
Average steepest K	7·18	7·11
Average flattest K	8·09	7·75
Mean astigmatism	0·91 mm radius (4·60 D)	0·64 mm radius (3·20 D)

Table 3 *Graft age and astigmatism*

Years	*Average astigmatism in D*
0–12 months	2·84
1–2 years	3·00
2–3 years	3·19
3–4 years	2·30
4–5 years	2·00
5–6 years	1·70
6–7 years	3·40
7–8 years	4·60
8+ years	2·80

SPECTACLES AND CONTACT LENSES

50% wore contact lenses; 40% wore spectacles; 10% needed no correction. The wearing of a spectacle lens was not necessarily associated with the degree of astigmatism or acuity but more often with contact lens tolerance, acuity, and the state of binocular vision.

It is axiomatic that patients with lower degrees of astigmatism and myopia would be able to wear spectacles. Therefore the average change in astigmatism in patients wearing contact lenses was compared with the group not wearing contact lenses. In those wearing contact lenses astigmatism reduction averaged 3·125 dioptres; in those not wearing contact lenses astigmatism reduction averaged 0·10 dioptres.

Conclusions

Less than 4% of the group were highly myopic (2 patients), and in both instances steep keratometry was not the reason. The average keratometry of the grafts was steeper than normal corneal curvature (7·8) after the sutures were removed by almost 0·2 mm, but after several months the tendency was towards a steeper curve to give the final average of 7·42, which cannot be considered keratoconic. There was a trend from an average astigmatism of just over 4 to a final 3·33. This almost agrees with the average keratometry recorded (see Table 1), and therefore the astigmatism measured by refraction agrees with the corneal curvatures. The axis of astigmatism was in most cases oblique, and remained so even several years after the operation. But extreme degrees of astigmatism showed a greater change towards normality than to be expected; moreover, in a few instances a complete change in axis was seen. Also of interest was the equal distribution of against and with the rule astigmatism. This all suggests that suturing has a great influence on maintaining curvatures of the graft, and that, once removed, corneas under severe stress gradually assume a trend towards the normal corneal curvatures.

Since almost an equal number of patients with grafts wore contact lenses for correction as wore spectacles, the most significant factor to emerge from the results was the marked decrease in astigmatism in the group wearing contact lenses as compared with those who did not. It is our practice to allow hard corneal lens or scleral lens wearers to obtain good acuity before the sutures are removed in some instances and, therefore, the lenses may be said to have a moulding effect on the graft which is beneficial.

We thank Wesley-Jessen, of Chicago, USA, for the loan of the PEK machine.

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Corneal thickness in extended wear of soft contact lenses

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SUMMARY The continual wearing of a soft contact lens for a period of 20 weeks is shown to produce no significant evidence of corneal swelling, although the use of soft lenses in conjunction with a topically applied solution is shown to produce evidence of transient swelling. The extent of corneal thinning during waking hours is also shown to be reduced among wearers of contact lenses for long periods.

Some corneal swelling invariable accompanies the wearing of contact lenses (Mandell and Polse, 1969). Such swelling is usually provoked by a disturbance to the available oxygen supply (Hill and Cuklanz, 1967), though other factors may also influence the cornea (Kempster and Larke, 1978).

In the present study the thickness of the cornea of patients wearing contact lenses without removal for a period of 20 weeks was examined. During the study it was intended to distinguish between those effects which were solely attributable to extended contact lens wear, and those effects which were attributable to extended lens wear in conjunction with proprietary solutions, as recommended by at least one manufacturer (Ganju, personal communication). For this reason 2 groups of lens-wearing subjects were examined in conjunction with a control group of non-lens wearers.

Patients and methods

Fifty-seven volunteer Caucasian subjects who came within a previously determined acceptance profile were assembled. One-third (the non-solution users' group) were fitted with a hydrogel lens manufactured from a copolymer of vinyl pyrrolidone and methyl methacrylate (Sauflon PW, manufactured by Contact Lens Manufacturing Ltd.). A further third (the solution users' group) were fitted with similar lenses that were removed and cleaned overnight at 8-week intervals with a proprietary cleaning agent (Monoclens and Monoclens C40, manufactured by Contact Lens Manufacturing Ltd.). In addition the solution users also instilled 1 drop of proprietary buffered saline on waking and before retiring each day (Sterilet, manufactured by Contact Lens Manufacturing Ltd.). The remaining third retained their spectacles and acted as controls.

At the 16th week of the study the right eyes of 7 volunteers from each group were monitored for change of corneal thickness during the period of 1 waking day (0900 to 2000 hrs). Corneal thickness measurements at 9 corneal locations (central: 15° and 30° in the vertical and horizontal meridians) were made with the aid of a self-recording topographic pachometer (Hirji and Larke, 1978).

The results from the pachometer were collected 'blind' by means of a tape printer. As the purpose of the study was to examine trends in the collected data, the readings were directly analysed instead of having a correction factor applied for an assumed corneal refractive index and a compensation factor for individual variations in corneal curvature. Hence the pachometer readings are given as 'apparent corneal thickness'.

A Latin square appointment system was used throughout the study, which ensured that each subject was examined once, at all appointment times, thus enabling the mean time of measurement to be kept constant for all subjects.

Results

TWENTY-WEEK STUDY

The analysed data for the 3 groups of patients showed a statistically significant ($P=0\cdot01$) pattern, which was equally reflected in all corneal regions. The results and regression equations for the central region of the cornea are shown in Fig. 1.

WAKING-HOURS STUDY

The results from the 3 groups of patients showed a statistically significant ($P=0\cdot01$) thinning of the

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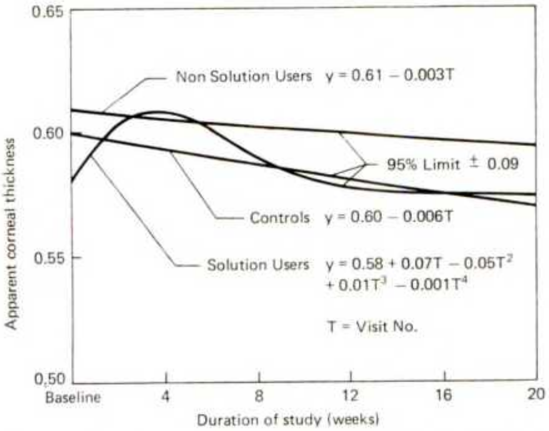

Fig. 1 *Human corneal thickness (central region) during a period of extended contact lens wear*

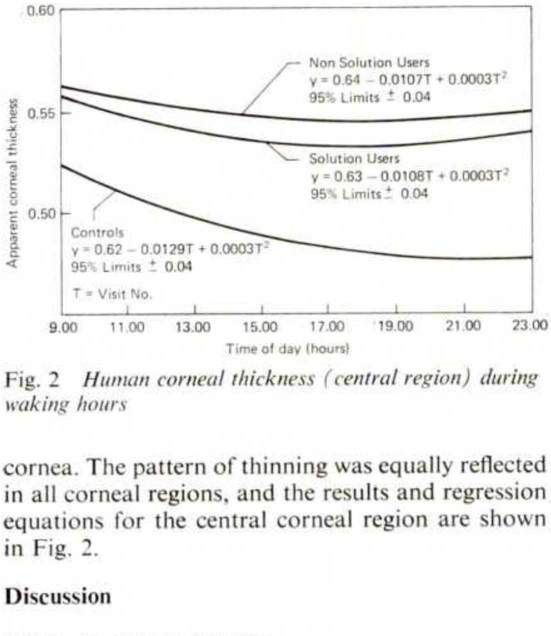

Fig. 2 *Human corneal thickness (central region) during waking hours*

cornea. The pattern of thinning was equally reflected in all corneal regions, and the results and regression equations for the central corneal region are shown in Fig. 2.

Discussion

TWENTY-WEEK STUDY

The results for the control and non-solution users' group indicate, a slight (4%) regular reduction in corneal thickness during the progress of the study. At present we have no entirely satisfactory interpretation for this result. The pachometer was calibrated before, during, and at the completiton of the study, and the data, which were collected 'blind' by means of a tape printer, showed no evidence of operator or instrumental bias. The study was conducted from January to June, and a seasonal variation may be plausible. However, it remains for further long-term work to investigate this possibility.

The data for the solution users' group show a pattern of transient swelling followed by a return to the prefitting norm. The absence of a similar pattern in the non-solution data suggests that the transient swelling is attributable to the solution used rather than to the presence of the contact lens. The solution used was 0·9% buffered saline, which was instilled daily. Hill and Terry (1978) have recently demonstrated the equivalent tonicity of the precorneal tear film to be 0·97%. Our currently preferred interpretation of the solution users' results is that the swelling was induced as a result of the change in tonicity commensurate with the instillation of saline. A check of stock records showed that no further saline was issued after the 10th week of the study, while an examination of returned patient questionnaires showed that the patients received no subjective benefit from the solution after an initial period and spontaneously gave up using them.

WAKING-HOURS STUDY

The results for the control subjects show a reduction in corneal thickness of approximately 8% during the waking day, while both groups of patients wearing contact lenses show a change of just under 3%. There is also an apparent difference between the initial values for the control and experimental groups, the experimental groups being some 5% thicker. An examination of prefitting values for all groups of subjects shows this difference to have arisen through a chance distribution between the groups rather than as a result of wearing contact lenses.

Our preferred interpretation of the difference in the extent of thinning between the groups is that it is due to the influence of the volume of water in the lens on tear tonicity levels. The change in tear tonicity as a result of evaporation has been held to be responsible for the rapid thinning of the cornea on lid opening (Mishima and Maurice, 1961; Mandell, 1965).

The influence of contact lens water volume on tear tonicity levels is summarised in Table 1. Hence

Table 1 *Influence of contact lens water volume on tear tonicity levels*

	Volume of tears (µl)	*Volume of water in lens (µl)*	*Tear loss through evaporation*	*% Change in fluid volume on the eye*	*Calculated tear tonicity (% NaCl)*
Non-soft lens wearer	7[1]	Nil	0·5[3]	7	0·96
Soft lens wearer	7[1]	Approx. 40[2]	0·5[3]	0·96	0·91

[1] Mishima (1965). [2] Authors' measured value. [3] Calculated from Mishima (1965).

among soft lens wearers tonicity provoked corneal thinning may be substantially absent, while slower changes attributable to other, as yet undetermined mechanisms may be seen (Kikkawa, 1973).

Conclusion

An examination of corneal thickness in wearers of contact lenses for extended periods shows a surprising absence of corneal swelling when contact lenses alone are used. However, the use of such lenses in conjunction with a topically instilled solution is shown to produce evidence of transient swelling, and it is probable that the role, and particularly the composition, of such solutions should be carefully examined. The degree of change in corneal thickness during waking hours is shown to be reduced for subjects wearing one type of high-water-content lens.

These results suggest a generally favourable level of physiological compatibility for this type of hydrogel contact lens worn through periods of sleep, and also emphasise the role of tear tonicity in passive corneal homeostasis.

The authors thank those members of staff and students of the University of Aston who participated in this study.

We would also like to thank Mr C. Peaston, senior electronics technician, for construction of the apparatus, and we are grateful to Contact Lens Manufacturing Ltd. for the supply of contact lenses, and for the financial support of one of us (N. K. H.).

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An animal model of *Fusarium solani* endophthalmitis

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SUMMARY Infection with *Fusarium solani* was established by injecting spores into the anterior chambers of outbred Wistar rats. The disease produced was remarkably similar to that reported in man and progressed to a fulminating endophthalmitis. Attenuation of the disease could be accomplished by repeated animal passage of the isolate.

The increasing frequency of ocular fungal infections over the past decade has spurred interest in the development of more effective therapy. Most efforts have been devoted to clinical studies because of the lack of a suitable animal model of progressive ocular disease. Although observations of clinical cases have demonstrated the promise of certain antifungal agents, only in a reliable animal model of the disease can the problems of effective therapy be successfully elucidated.

Fusarium solani has recently emerged as an important ocular pathogen (Jones, D. B., *et al.*, 1969; Gugnani *et al.*, 1976), and a number of attempts have been made to establish an animal model. Transient disease has been produced in the rabbit but could not be maintained for more than a few days (Jones, B. R., *et al.*, 1969). Recently a more prolonged but still self-limiting disease has been reported in the rabbit pretreated extensively with corticosteroids (Forster and Rebell, 1975). Moreover Burda and Fisher (1959) reported the development of fusarial corneal infection in a corticosteroid treated rat. Despite the increased rate of infectivity in these models, a major criticism is the use of a compromised host.

The failure to develop a progressive eye infection in the normal animal emphasises the complexity of the problem. A number of factors involving the infecting organism and its interaction with the host animal appear to be important in this regard. In addition to variable pathogenicity of individual strains, maintenance of virulence in the laboratory is a major problem. Selection of an appropriate host animal is crucial. In this paper we report our experience with fungal endophthalmitis due to *F. solani* in the normal rat.

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Material and methods

SPORE SUSPENSION

Spores from *F. solani* isolates from human corneal ulcers were harvested by sterile loop from blood agar plates that had been incubated at 34°C for 3 to 4 days. The spores, suspended in sterile saline, were pipetted into a sterile tube and centrifuged for 10 minutes. After discarding the supernatant, fresh saline was added, and a second centrifugation was performed. The spore suspension was then brought to a total volume of 2 to 3 ml with sterile saline and counted by haemocytometer. Viable spore counts were determined by plating specific volumes of serial 1:10 dilutions in triplicate on to blood agar plates. These plates were incubated for 2 days at 34°C. Colony counts usually indicated at least 90% viability of the inoculum. Since *F. solani* cultures tend to lose their ability to sporulate with sequential passage, spores from the initial isolates were frozen for future use. Vials of these frozen spores were used periodically as required to ensure maximum sporulation. Fresh spore suspensions were made up to a concentration of 10^8 or 10^7/ml. Heated, killed spores and spores from isolates that had undergone animal passage 1 to 3 times were also used.

ANIMALS

Outbred Wistar rats of 200 to 300 g weight were used in our experiments and maintained for various intervals up to 3 weeks after inoculation.

INOCULATION TECHNIQUES

A 30-gauge needle was connected by plastic tubing to a 1 ml Hamilton gas type syringe, 1001-LT, fitted to a device which enabled us to dispense 0·02 ml of spore suspension per injection. The rats were anaesthetised with an intraperitoneal injection of 0·25 ml of pentobarbitone sodium. With the operating micro-

Table 1 *Effects of inoculation with* F. solani

Inoculum, spores	*Number of animals*	*Culture positive, total cultures*	*Histology positive, total observed*	*Observations of inflammation*		
				Acute/progressive	*Transient*	*None*
10^8/ml	78	33/38	27/30	61	10	7

scope for visualisation the 30-gauge needle was introduced into the anterior chamber through the peripheral cornea, and the spore suspension was injected. The spores could easily be seen entering the eye. Care was taken to ensure that the injection of the spores was performed as atraumatically as possible. If the tip of the needle touched the iris or lens or the injection was inadvertently delivered into the posterior chamber or the chamber became flattened after withdrawal of the needle, the animal was removed from the study. After each injection an aliquot was dispensed from the syringe for total spore counts and viability counts.

Biomicroscopic examination was performed on the rats 2 to 3 times a week, and the animals were killed at varying intervals over the ensuing 4 weeks. Eyes were submitted for culture and histopathological examination.

CULTURAL AND HISTOPATHOLOGICAL TECHNIQUES

We experimented unsuccessfully with several methods of obtaining material from each eye for simultaneous culture and histopathological examination. Therefore pairs of eyes matched for similarity of clinical disease were submitted for culture and histology. Eyes selected for culture were ground in sterile tissue grinder tubes, and the resulting fine suspension was cultured on blood agar, Sabouraud's agar supplemented with 100 μg/ml of gentamicin and 1% yeast extract, thioglycolate medium supplemented with gentamicin, and brain-heart infusion broth supplemented with gentamicin. All cultures were incubated at room temperature. Plates were observed for up to 2 weeks if necessary. Broth cultures were incubated on a rotary shaker.

HISTOLOGY

Eyes selected for histological examination were fixed in Bouin's fluid or 10% buffered formalin. Sections were stained with haemotoxylin and eosin, methenamine silver, and periodic acid Schiff.

Results

EXPERIMENT 1

F. solani spores, in a concentration of 10^8 spores/ml, were injected into the anterior chamber of one eye in 78 rats. The eyes were observed for 3 weeks, the animals were killed at varying intervals, and the eyes were subjected to either fungal culture or histopathological examination.

CLINICAL OBSERVATIONS

Within 24 to 48 hours of inoculation a yellowish exudate developed on the iris adjacent to the pupil. Frequently associated with this was a posterior chamber hypopyon visible through the transparent iris. In some animals the exudate on the iris spread so that it partially or completely occluded the pupil. Corneal oedema developed as the chamber rapidly became shallower over the following few days. The eye then began to enlarge. However, in most animals with a posterior chamber hypopyon the inflammation remained posterior to the iris involving lens and vitreous. As the inflammation progressed, the anterior chamber became shallow and the eye enlarged. The time period for this course of events was rapid, usually from 3 to 10 days, but the process was usually well established by 7 days. In most of the animals the inflammation was so fulminating that a large proportion had to be killed prematurely. In 61 of the 78 animals this rather typical acute progressive anterior segment inflammation, with shallowing of the chamber, corneal oedema, and ocular enlargement developed. In 10 there was a mild to moderate inflammation of the anterior segment but the anterior chamber remained of normal depth. In 7 eyes there was no evidence of inflammation during the period of observation.

Overall, *F. solani* was isolated from 34 of 38 eyes cultured, while 27 of 30 matched eyes showed histological evidence of fungal replication based on the presence of hyphal elements in ocular tissue (Table 1). A disproportionate number of the animals were killed in the first week because of the severity of the inflammation. Table 2 summarises the results

Table 2 *Isolate from human disease*

Days after inoculation	*4*	*7*	*14*	*21*
Number of eyes	13	15	17	5
Positive cultures	6	7/9	12/14	1/2
Positive histology	7	3/6	2/3	3

Table 3 *Effect of animal passage on clinical disease*

		Animal passage		
Inoculum	*Fresh isolate*	*X1*	*X2*	*X3*
Number of eyes	15	8	4	4
Severe progressive inflammation	14	2	1	0
Culture positive	6/6	1/1	0/1	—
Histology positive	6/7 (Day 4–15)	0/1 (Day 8)	— (Day 4)	—
Mild to moderate inflammation	1	6	3	4
Culture positive	0/1	3/3	2/2	2/4
Histology positive	— (Day 21)	2/3 (Day 8–21)	1/1 (Day 7–11)	— (Day 14)

in animals killed at days 4, 7, 14, and 21 only. The fungus was recovered from 12 of 14 eyes cultured at 2 weeks.

EXPERIMENT 2

In an attempt to reduce the severity of the inflammation the concentration of inoculum was reduced to 10^7/ml. The experimental technique was otherwise identical. In contrast to the previous experiment we were unable to produce disease in 21 of the 31 inoculated eyes, and in the remainder 2 were culture positive and 4 were histologically positive for fungal infection.

EXPERIMENT 3

Since animal passage may reduce the virulence of the organism and therefore the severity of the ocular disease, spores harvested from an isolate from human corneal disease were passaged 3 times in rat eyes. Inocula were prepared for injection from isolates after each passage. Thus, we compared the disease produced by the fresh isolates with that produced by the same isolate after 1, 2, and 3 animal passages. The results are shown in Table 3. The original human isolate produced severe progressive inflammation, so that it was necessary to kill all but one of the animals in the first 2 weeks. Animal passage caused marked attenuation in the disease process, so that it could now be classified as mild to moderate. Nonetheless, recovery of the isolate by culture or histological confirmation of a fungal infection continued to occur in a high percentage of the animals (Table 3). We were unable to show that repeated animal passage had a greater attenuating effect than a single passage.

EXPERIMENT 4

The injection of heat inactivated spores into 11 eyes produced a transient severe inflammation in 3 eyes and minimal inflammation in 2, and the remaining 6 eyes were unaffected. All cultures were negative for fungi.

HISTOLOGICAL CONFIRMATION OF FUNGAL INFECTION

Histological examination revealed the presence of hyphal fragments in a variety of ocular structures in 27 of 30 eyes. The fungus showed an overwhelming tendency to localise in the posterior chamber of the rat eye and lens, but was also found invading the vitreous, iris, ciliary body, anterior chamber, and cornea. The histological features will be discussed in more detail in a forthcoming paper (in preparation).

Discussion

An animal model of human infectious disease must meet certain criteria. It should simulate the human disorder and be precise and reproducible. The disease should be progressive rather than self-limited and should be accessible to clinical and laboratory investigation. Finally, modification of the host, for example, by immunosuppression, should be avoided if at all possible.

The rat model of infection with *Fusarium solani* appears to meet these criteria. In these experiments the animals developed an endophthalmitis that was remarkably similar to the human disease, although somewhat more severe (Gugnani *et al.*, 1976). Nonetheless, it was sufficiently even-paced to permit sequential clinical observations to be made. Animal passage of the isolate performed to decrease its virulence was successful in attenuating the clinical disease, but reduction in the concentration of the inoculum resulted in failure to establish an ongoing infection in most animals.

Although the rat eye is small, it is easily examined by slit lamp. The transparent iris permits some assessment of the inflammatory changes in the posterior chamber, including the development of hypopyon—a unique observation, we believe. Studies are now under way to evaluate the various forms of therapy of infection with *F. solani* through the use of this model.

This study was supported in part by Public Health Services grant EY-01621 and a grant from Research to Prevent Blindness Inc.

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Book reviews

Microsurgery of the Anterior Segment of the Eye. Vol. 2. The Cornea: Optics and Surgery. By RICHARD C. TROUTMAN. Pp. 357. £39·90. Mosby: St. Louis, Missouri. 1977.

This book, the second in Professor Troutman's series on anterior segment microsurgery, deals with corneal problems. The author first considers the surgical anatomy and optics of the cornea; the latter section is particularly concerned with changes brought about in the cornea by disease or surgery. The next section details the indications for keratoplasty in relation to anatomical, topographical, and optical variations which may affect the cornea. Chapters are included on obtaining, processing, preparing, and cutting donor material; the technical aspects of keratoplasty, both penetrating and lamellar; modifications in technique in the management of aphakia; surgical techniques to obtain a better optical result such as wedge resection; and operative treatment of glaucoma in a grafted eye. There is a final chapter on routine postoperative care and treatment of complications.

This is a comprehensive account of one author's experience of corneal surgery. It is beautifully illustrated by line drawings emphasising every aspect discussed in the text. The basic techniques described will be of interest to the beginner in corneal surgery, while the refinements planned for better optical results will prove of greater interest to the experienced surgeon. RICHARD PACKARD

Neuro-ophthalmology. By JOEL S. GLASER. 1978. Pp. 364, figs., tables, refs. Harper & Row, Hagerstown, Maryland ($35)

This symposium from the University of Miami and the Bascom Palmer Eye Institute is a collection of essays written by experts in their own field. Amaurosis fugax is discussed by Noble David, who comes to the conclusion that our ultimate hope of controlling this disease lies in a better understanding of the pathogenesis of atherosclerosis and early application of prophylactic principles. Scheinberg, talking on management of occlusive cerebrovascular disease, states that the thrust of recent research into the biochemistry and physiology of cerebral ischaemia has been to identify those events responsible for tissue death and to develop pharmacological strategies to counteract them. He feels there is good reason to assume that ultimately these approaches will be transferable to the bedside. Daroff, in discussing dizziness and vertigo, hopes that further experience will establish a safe and reliable operation for these intractable patients whose situation is indeed desperate. Troost, in a chapter on aneurysms, arteriovenous malformations, and fistulas, sums up our present knowledge on this aspect of cerebral disease. Rhoton and his colleagues discuss microsurgical anatomy of the sellar region and cavernous sinus in a most unusual way, stressing how the variants of anatomy are so important in modern cerebral surgery, and this is followed by a discussion on microsurgery of the sellar region reminiscent of the transformation which is taking place in ophthalmic surgery. Transsphenoidal approach to the sella is concisely described by Linda Orr and associates.

Axonal transport in the retina and optic nerve is discussed by Douglas Anderson, and this is followed by an assessment of intraconal steroids in the treatment of retrobulbar neuritis by Alan Bird and his colleagues. Endocrine ophthalmopathy is described independently of laboratory confirmation but supported by characteristic findings on the computer scanner and ultrasound recordings of the orbit.

Schmidt discusses saccadic eye movements in myasthenic ocular muscle pareses, and then a chapter follows on postganglionic Horner syndrome by Grimson and Thompson. The practical management of pseudotumour cerebri is discussed by Lubow, and this is followed by a chapter by Bell on observation of retinal nerve fibre degeneration after optic nerve injury. A stimulating discussion on changing concepts of structure and function in pituitary adenomas is offered by Landolt, and a chapter follows on therapeutic aspects of the empty sella syndrome. The final chapters are on inferior hemianopia in parasellar and pituitary tumours and one on visual field defects associated with choroidal folds. This book can be read chapter by chapter, one at a time. Each is a complete story in itself. S. J. H. MILLER

Atlas of Veterinary Ophthalmic Surgery. By STEPHEN I. BISTNER, GUSTAVO AGUIRRE, and GEORGE BATIK. 1977. Pp. 302, figs., tables, refs. Saunders, Philadelphia (£22·50)

This book is a further addition to the increasing library on veterinary and comparative ophthalmology. It is, however, by far the best volume dealing with operative surgery, and although primarily intended for practising veterinary surgeons and students it will be of interest to some ophthalmic surgeons. The authors are 2 well-known American veterinary ophthalmologists, together with a medical illustrator from the New York State Veterinary College. They describe the basic techniques applicable to a variety of animal species, though the major part of the book is devoted to the dog, as could be expected.

The first 3 chapters deal with instruments, anaesthesia (unfortunately without reference to techniques of general anaesthesia for ophthalmic surgery), and basic techniques including plastic surgery, eye exposure, etc. The remaining 8 chapters cover the eyelids, entropion and ectropion, the nasolacrimal system, conjunctiva and membrana nictitans, cornea, lens, glaucoma, and the orbit. These chapters clearly describe many surgical procedures and include useful notes on practical anatomy and physiology, complications, and postoperative treatment. There are no photographs except in the introductory chapters, but many black-and-white pen-and-ink drawings of good quality are included. Each chapter finishes with several references, mainly from American veterinary journals.

There are 3 appendices: a useful table of the breed predisposition to eye diseases in dogs and cats; a colour atlas of some common ocular conditions almost entirely in the dog; and a list of American manufacturers.

K. C. BARNETT

Notes

Iowa Eye Association

A meeting will be held at Iowa City, Iowa, USA, on 7–9 June 1979, when the following subjects will be discussed: (1) Concepts in the evaluation and management of penetrating ocular trauma. (2) The role of vitrectomy in penetrating ocular trauma and other conditions. (3) Macular degeneration—pathogenesis and evaluation. There will be a neuro-ophthalmology symposium on evaluation of the optic nerve and the pupil. Details from Thomas A. Weingeist, MD, Department of Ophthalmology, University of Iowa Hospitals, Iowa City, Iowa 52242, USA.

Colour vision deficiencies

The fifth symposium of the International Research Group on Colour Vision Deficiencies will take place at St. Mary's College, Strawberry Hill, Richmond-upon-Thames, on 26–28 June 1979. The special themes will be (1) The neuroanatomy of colour vision processes; (2) colour vision at high luminances; (3) colour vision in relation to other visual functions in clinical ophthalmology. The guest speakers will be Professor H. G. Sperling, Dr W. S. Stiles, and Dr Vivianne Smith Pokorny. Further information from the organising secretary, Mrs J. Birch, 5 Stuart Grove, Teddington, Middx TW11 8RR.

Echo-ophthalmology

A course covering A-scan, B-scan, and Doppler echography in intraocular and orbital disease will be held on 26–30 June 1979 at the university eye clinic in Vienna. Details from Dr Peter Till, II Universitätsaugenklinik, Alserstrasse 4, A-1090 Wien, Austria.

Subretinal space

A meeting on the subretinal space is scheduled to take place in Kibbutz Kirgat, Jerusalem, on 14–19 October 1979. All interested participants may send papers related to anatomy, physiology, biochemistry, experimental pathology, and clinical aspects to Dr Hanan Zauberman, Hadassah University Hospital, Eye Department, Jerusalem, Israel.

Retinal therapy and diagnosis

A 5-day advanced course on techniques of retinal diagnosis and therapy will be held at the Institute of Ophthalmology, Cayton Street, London EC1V 9AT, on 26–30 November 1979. Application forms from: The Clinical Subdean, Institute of Ophthalmology, 17–25 Cayton Street, London EC1V 9AT. The course fee is £70.

Herpetic eye disease

An international symposium on herpetic eye disease will be held at Freiburg on 12–14 April 1980. Information and forms for abstracts will be issued about 1 September 1979. Further details from Dr Rainer Sundmacher, Universitätsaugenklinik, Killianstrasse, D-7800 Freiburg, West Germany.

Ophthalmological Society of the United Kingdom

The centenary meeting of the Society will be held in London at the Institute of Education on 16–18 April 1980, preceding the European Ophthalmological Society Congress in Brighton, 21–25 April 1980 with the intermission of the weekend. The meeting will be inaugurated by a thanksgiving service in academic robes at Westminster Abbey to which royalty and many notables will be invited. It is hoped that members will give their full support to this historic occasion and provisionally reserve the dates of this meeting. Full details from The Honorary Secretary, Ophthalmological Society of the United Kingdom, Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

European and UK Ophthalmological Societies

The Sixth Meeting of the European Ophthalmological Society will be held in Brighton, England, on 21–25 April 1980. The main theme will be 'The Cornea in Health and Disease'. Subsidiary meetings on other subjects will be held in association with the main meeting, which will include round-table discussions and workshop sessions. Papers should be submitted to Professor W. S. Foulds, Department of Ophthalmology, University of Glasgow, Glasgow, Scotland. Further information can be obtained from the Official Organiser, Holland Organising Centre, 16 Lange Voorhout, The Hague, Netherlands.

The Centenary meeting of the Ophthalmological Society of the United Kingdom will be held in London during the week preceding that of the European Society Meeting in Brighton, 16–18 April 1980. Further information for this meeting can be obtained from the Honorary Secretary, Ophthalmological Society of the United Kingdom, Royal College of Surgeons, Lincoln Inn Fields, London WC2.

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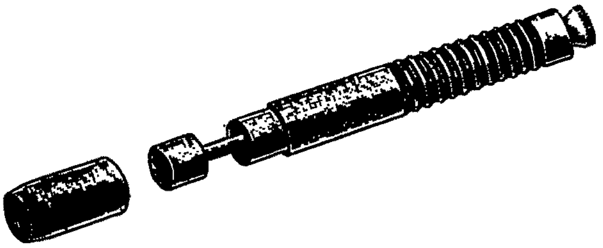

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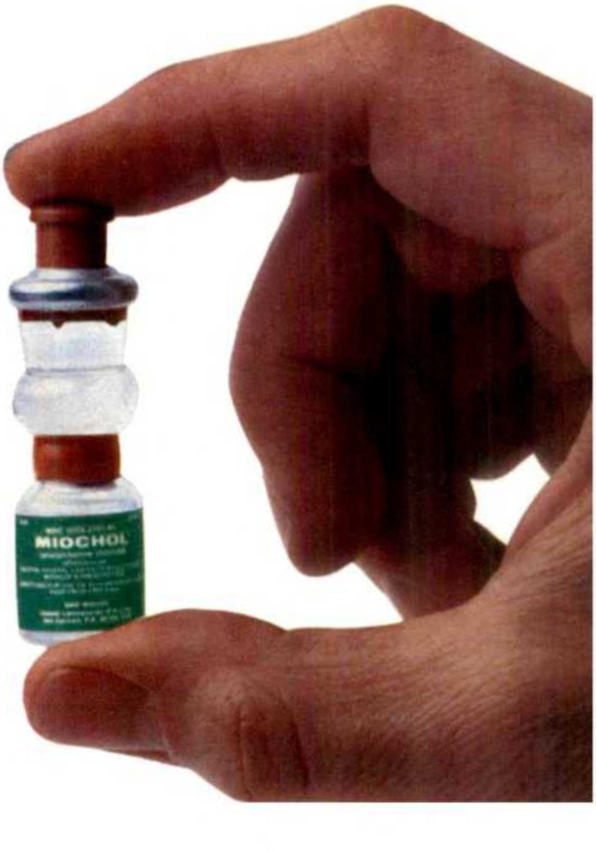

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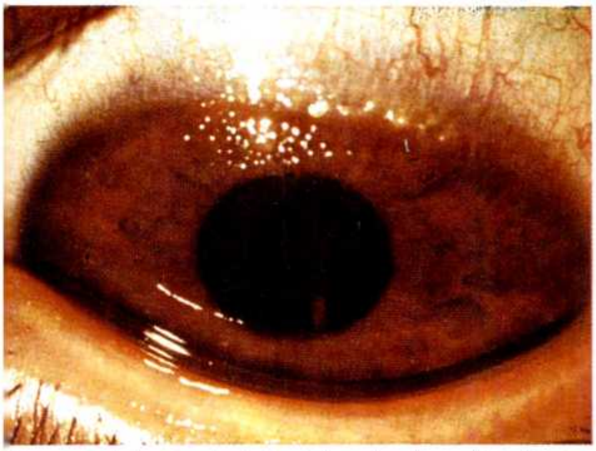

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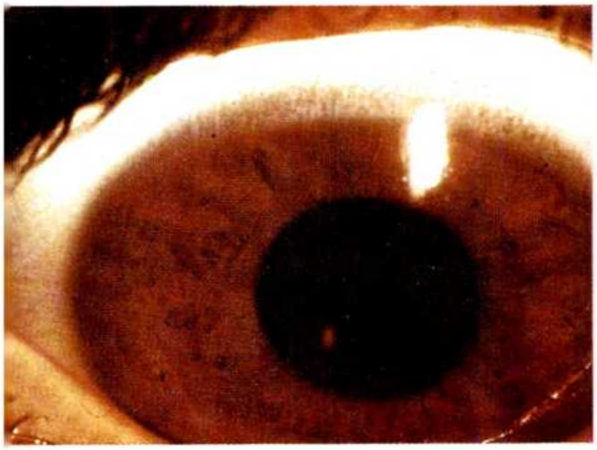

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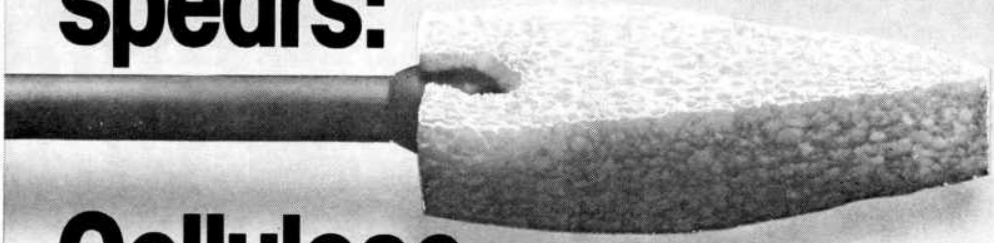

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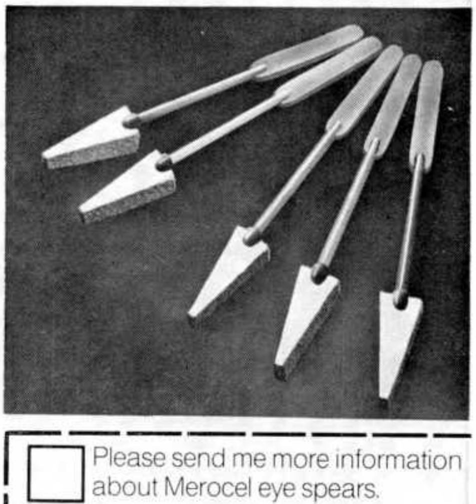

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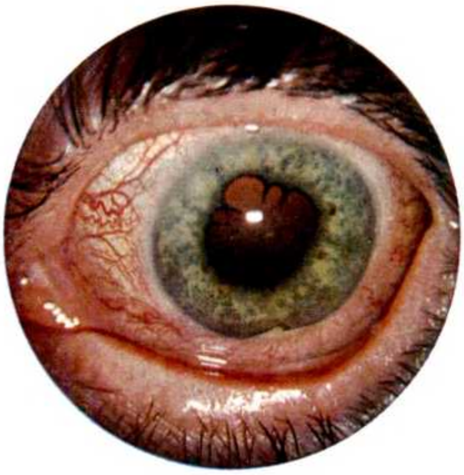

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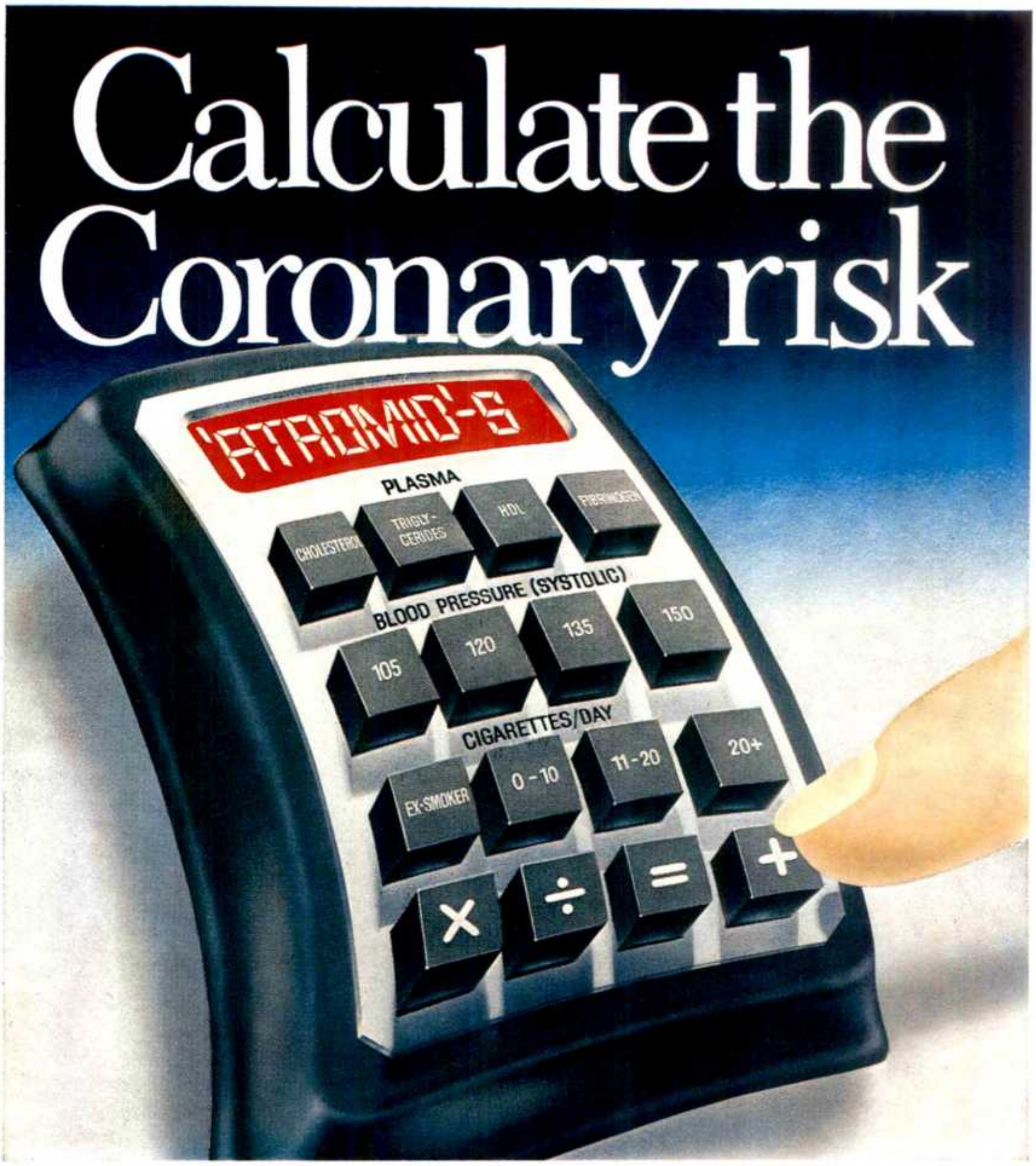

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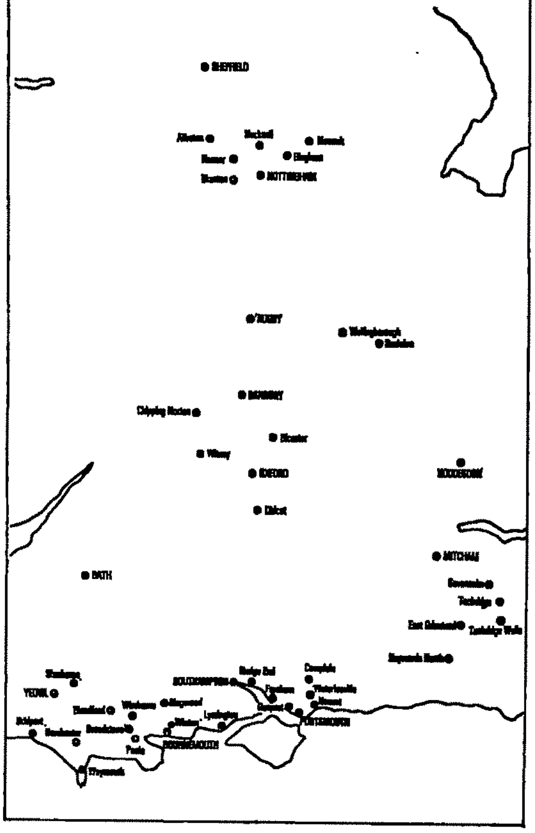

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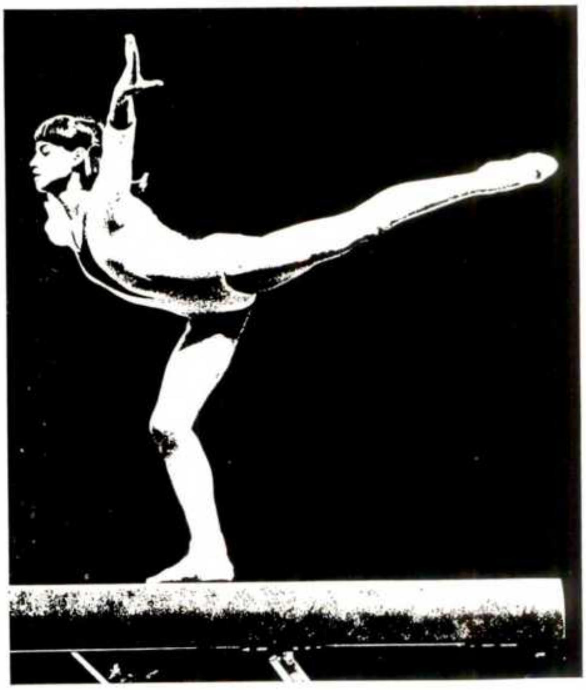

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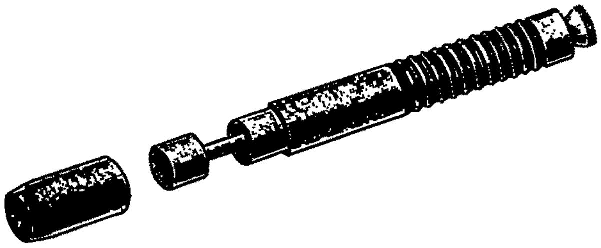

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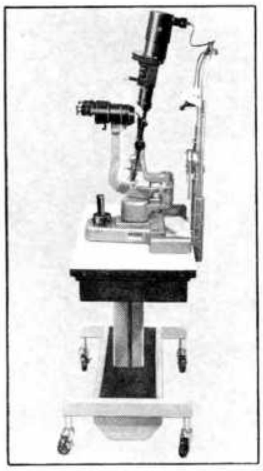

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HLA and eye disease

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SUMMARY This review article discusses the evolution and function of the histocompatibility system, the nature of the HLA antigens and their classification, the phenomenon of linkage disequilibrium, and the mechanisms of HLA and disease susceptibility. The reported associations between HLA antigens and various eye diseases are analysed and their significance is discussed. Problems in designing studies on HLA and disease associations are highlighted and suitable statistical procedures for the analysis of the results are outlined.

When first introduced by an international committee sponsored by the World Health Organisation the term HLA stood for antigens associated with *h*uman *l*eucocytes at the genetic locus *A* (that is, first locus). Since this antigenic system has now been found to consist of more than one locus of interconnected sets of genes, HLA is now used to cover the entire group of histocompatibility or transplantation antigens. These antigens are surface glycoproteins which occur not only on leucocytes but also on other nucleated cells, platelets, and reticulocytes. If these antigens are removed by enzymes in vitro the cell can reconstitute them within 6 hours, which indicates their rapid turnover. It is not surprising, therefore, that small amounts are continuously released into the plasma. Embryological studies have shown that these antigens can be detected in fetal tissues as early as the sixth to eighth week of gestation. Every individual possesses these cell membrane antigens as a direct expression of his or her genotype, and it is therefore not surprising that they differ from one person to another, the differences being greatest between members of unrelated families.

Classification

Much of our understanding of the human HLA system comes from studies in mice in which the major histocompatibility system known as H-2 evokes a particularly strong response in an allogeniec host, that is, members of the same species, and outweighs all other systems in promoting graft rejection. HLA, the comparable major histocompatibility system in man, probably comprises more than 70 different antigens (Table 1). Those which have not been unequivocally demonstrated and whose separate identity is still debatable are called w (workshop) antigens. The development of this group of transplantation antigens appears to be controlled by 5 adjacent loci on the major histocompatibility region of each of the pair of autosomal chromosome 6 (Fig. 1). Consequently each cell

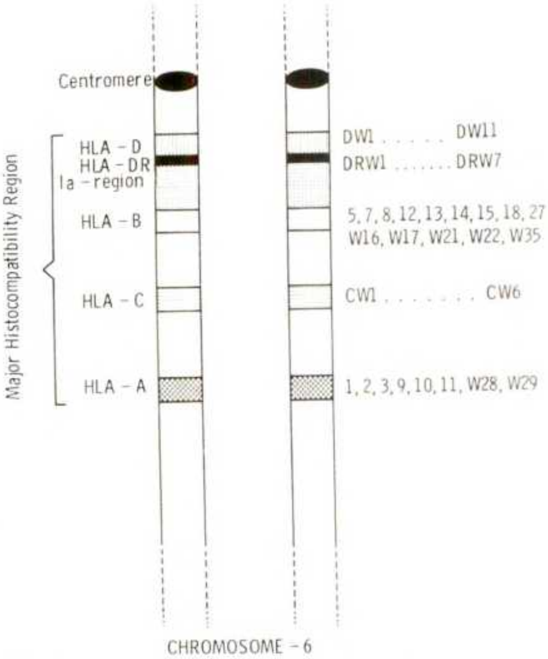

Fig. 1 *Genetic determinants of the major histocompatibility antigens. Each of a pair of autosomal chromosome 6 possess 5 adjacent loci which carry the genes responsible for the formation of HLA antigens*

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Table 1 *Classification of HLA antigens*

Locus A		*Locus B*		*Locus C*	*Locus DR*	*Locus D*
HLA A1		HLA Bw4		HLA Cw1	HLA DRw1	HLA Dw1
A2		B5	Bw51	Cw2	DRw2	Dw2
A3			Bw52	Cw3	DRw3	Dw3
A9	Aw23	Bw6		Cw4	DRw4	Dw4
	Aw24	B12	Bw44	Cw5	DRw5	Dw5
A10	Aw25		Bw45	Cw6	DRw6	Dw6
	Aw26	B14			DRw7	Dw7
A11		B15				Dw8
Aw19	A29	Bw16	Bw38			Dw9
	Aw30		Bw39			Dw10
	Aw31	B17				Dw11
	Aw32	Bw21	Bw49			
	Aw33		Bw50			
	Aw34	Bw22				
A28		B27				
Aw36*		Bw35				
Aw43*		B37				
		B40				
		Bw41				
		Bw42*				
		Bw46†				
		Bw47				
		Bw48				
		Bw53				
		Bw54†				

*Found only in black population. †Found only in mongoloid population

membrane in a heterozygous individual may contain a maximum of 10 different antigens (Bodmer, 1978; Gill *et al.*, 1978). The HLA antigens most commonly associated with the first, that is, A, locus include HLA A1, A2, A3, A9 (which is now divisible into Aw23 and Aw24), and HLA A10 (which has been split into A25 and A26), while prominent among the antigens controlled by the second (or B) locus are HLA B5 (comprising Bw51 and Bw52), HLA B7, B8, and B27. The third serologically determined locus codes provisionally for about 6 different antigens designated HLA Cw1 . . . HLA Cw6.

Grafts bearing various HLA antigens give rise to humoral antibodies in an allogeneic host and can therefore be detected by serological methods using sera derived from such sources as multiparous women who have developed antibodies to their offsprings' paternally derived antigens, from recipients of multiple blood transfusion, from immunised volunteers, and from patients who have previously rejected an incompatible graft. Categorisation of HLA antigens at loci A, B, and C is usually performed by exposing suspensions of patients' lymphocytes to a battery of specific antisera in the presence of rabbit complement and looking for evidence of cell lysis.

In addition to these histocompatibility antigens detected by serological methods (that is, serologically determined 'SD' antigen) there are other HLA antigens which can be detected only by incubating donor lymphocytes with lymphocytes of the proposed recipient (mixed lymphocyte culture) and examining for evidence of blastic transformation and division. More recently a panel of homozygous typing cells (HTC) have been used to detect these lymphocyte-defined (LD) antigens, which are controlled by the locus D on the major histocompatibility region and are designated HLA D. These consist of about 11 different provisional antigens (HLA Dw1 . . . Dw11).

There is considerable evidence indicating the existence of another HLA locus which is closely linked with the D locus antigens and is therefore called HLA DR (that is, D related). The corresponding antigens can be detected, however, by serological methods and have been designated HLA DRw1 . . . DRw7. It is of interest that, although HLA A, B, and C antigens are expressed on the surfaces of almost all cells except erythrocytes, spermatozoa, and placental trophoblasts, the HLA DRw antigens have a restricted tissue distribution, being present only in B lymphocytes, in monocytes, and in the Langerhans cells of the skin. The biological implications of this restricted expression are discussed later.

Biochemistry of HLA antigens

The HLA A, B, C, and DRw antigens are insoluble in traditional aqueous solvents owing to the presence of a small hydrophobic domain in the molecule which is inserted in the lipid bilayer of the cell membrane. The HLA A, B, and C antigens consist of a single glycosylated polypeptide of 43 000 molecular weight which is non-covalently linked to another distinct polypeptide $\beta 2$ microglobulin. The HLA DRw antigens on the other hand comprise two distinct glycosylated polypeptides of molecular weights 28 000 and 33 000. The human DRw antigens thus resemble mouse and guinea-pig Ia (immune associated) antigens. The precise biochemical nature of HLA D antigens is not clear.

It has been calculated that more than 300 million genetically different individuals can be formed by the known alleles of the HLA A, B, C, and D loci, and of these more than 30 million will have distinguishable combinations of antigens. Sometimes alleles at different loci occur together on the same chromosome more often than is expected by chance. This tendency is called 'linkage disequilibrium' and is of importance in studies on mechanisms underlying HLA and disease association. Thus, A1 often exists with B8, A3 with B7, B7 with Dw2 and DRw2, B8 with Dw3 and DRw3, B12 with Dw2, and B15 with Dw4. Furthermore, in any study on HLA and disease association it is important to realise that, although certain antigens, for example, HLA A2, are present at a relatively high frequency in populations all over the world, some may have a restricted distribution probably related to evolution and survival of the fittest. Thus, A1, A3, A28, A29, Aw30, and Aw32 are absent in Japanese, whereas A11 is not found in African blacks, who have Aw43 and Bw42, which is not found in other races.

Biological role of HLA antigens

It seems unlikely that HLA antigens were developed to outmanoeuvre the transplantation surgeon, and, although it has been speculated for some time that they facilitate immune surveillance and consequent destruction of mutant tumour cells having a different set of such antigens, it has only recently been possible to show that they play an important role in the normal immune response. It has also been postulated that a large number of antigenic receptors shared by different classes of lymphocytes might be the outcome of lymphoid cells in early embryogenesis responding to host transplantation antigens by undergoing division and somatic mutation. The major histocompatibility region in mice incorporates loci concerned with immunological responsiveness—the so-called Ir genes—and if similarly true of the human species such a relationship could help to explain the concomitance of several diseases such as ankylosing spondylitis and acute anterior uveitis in which there may be an intrinsic immunological dysfunction with the presence of specific HLA antigens.

It is known that an immune response to most of the antigens requires co-operation between macrophages, helper T cells, and B lymphocytes before differentiation of the latter into plasma cells. For a successful interaction it is essential that the helper T cells react simultaneously with the antigen as well as the HLA DR antigens (Ia in mice) on the surface of a macrophage or a B lymphocyte. T cells with suppressor activity are essential for the regulation of immune response, and studies have shown that HLA compatibility is essential for this effect.

Furthermore, it is inferred from studies in mice that cytotoxic T cells in man appear to use antigens determined by HLA A and B loci for recognition and subsequent killing of their targets. It would appear that, although the biological role of HLA in immune functions is largely inferred from evidences obtained in animals, there is no doubt that histocompatibility gene products modulate lymphoid cell interactions and are responsible for recognition and handling of antigen.

HLA and disease susceptibility

It is well established that over 90% of patients with ankylosing spondylitis show the presence of HLA

B27, and a normal person who is positive for this antigen is about 100 times more at risk of developing this disease than a B27-negative person. At the same time it is also true that, although nearly all patients with ankylosing spondylitis may have B27, only a relatively small proportion of people with B27 ever suffer from the disease. The question therefore arises how a particular HLA antigen increases the susceptibility of an individual to a particular disease and what other factors act in concert to determine the final outcome. Although the precise mechanism of HLA and disease susceptibility is still enigmatic the following hypotheses may explain some of the possibilities.

(*i*) There is a molecular mimicry between some components of the infecting organism and one of the HLA antigens. This would lead individuals having the relevant antigen being unable to mount an immune response to the pathogen, as indeed to self antigens. This would allow infection to occur and might encourage persistent infection with organisms that will otherwise be eliminated. Evidence has been presented in favour of this form of cross tolerance, and it has been shown that antibodies raised against klebsiella react only with HLA B27+ve lymphocytes. This supports the idea that ankylosing spondylitis and acute anterior uveitis develop as a result of infection with this group of organisms in individuals who do not recognise klebsiella antigens (Seager *et al.*, 1979).

(*ii*) It has been suggested that certain HLA antigens may act as cell-membrane receptors for pathogens, thus allowing them a strong foothold. There is as yet little experimental evidence to support this view. It is possible that the relevant HLA antigens are later modified by the organism and mount an autoimmune inflammatory reaction.

(*iii*) It has also been proposed that in some diseases certain HLA antigens may in some way play a limiting role on the efficiency with which T lymphocytes and macrophages recognise determinants on a particular pathogen.

(*iv*) However, it is possible that HLA antigens themselves play an insignificant role in disease susceptibility, but they may be linked to several putative immune-response genes which are responsible for variations in specific immune responses to pathogenic micro-organisms.

HLA studies: design and evaluation

When conducting studies on HLA and eye disease it is important to recognise the problems that can arise both in the designing of studies and in the analysis of the results. Disregard of these ground rules may, and in fact has, led to a series of reports on HLA association with glaucoma, retinoblastoma, and other eye diseases which have later been invalidated by more careful studies (Damgaard-Jensen and Kissmeyer-Nielsen, 1978).

It is important, for example, to give due attention to proper selection of controls, which must include consideration of age, sex, race, exposure to environmental factors, and possible triggering events. A disease of multifactorial aetiology might not show clear HLA and disease inheritance patterns, because coexistence of several genes might be prerequisite for the manifestation of the disease state. This may be the case in some of the negative reports in those eye diseases such as retinitis pigmentosa in which there is otherwise evidence of a genetic linkage.

Problems may arise both with the sera and the cells used for HLA typing. A very potent antiserum, for example, may in fact be multispecific, and some of the antibodies may thus be detecting non-HLA antigens. Furthermore, lack of sufficient sera for some allelic specificities can bias results if it leads to false assignment of antigens.

In the analysis of the results some of the statistical errors and shortcomings deserve emphasis because of their great importance (Edwards, 1974; Svejgaard *et al.*, 1974; Dick, 1978).

(*i*) Linkage disequilibrium may provide spurious associations unless recognised. Thus, HLA A1, which is often found in association with HLA B8, may be spuriously associated with some diseases in which in fact the frequency only of HLA B8 is increased. Multiple comparisons will dilute the significance of such associations.

(*ii*) If an HLA association is sought, with significance around the 5% value, then if 20 or more HLA antigens are tested there is a purely random chance that one of the antigens may be altered in frequency (1 in 20 = 5%). It has been suggested that the statistical significance in such situations can be corrected by multiplying the P value with the number of separate specificities tested (Woolf, 1955). Thus in one study (Zimmerman *et al.*, 1977), in which increased frequency of HLA B5 was reported in association with herpetic keratitis ($P<0·01$), the P value after correction (Pc) appears to be insignificant ($P<0·3$).

(*iii*) Since HLA antigen prevalences, unlike many other histochemical data, are not independent events, many statisticians believe that the method recommended by Woolf is too conservative and may not be strictly correct. It has been recommended, therefore, that either the findings should be compared with another published report or a second series of cases should be evaluated in the light of the results from the first series.

(*iv*) Once the association of a particular HLA

Table 2 *HLA association with diseases of ophthalmic importance*

Disease	*Antigen*	*Frequency percentage*		*Relative risk*
		Patients	*Controls*	
Behçet's disease	HLA B5	60	28	3·86
Vogt-Koyanagi-Harada syndrome	HLA Bw54	45	13	5·4
	HLA Dwa	67	16	10·5
Malignant melanoma of the choroid	HLA Aw32	11	3	4
Acute anterior uveitis	HLA B27	43	7	10
Diabetic retinopathy (juvenile)	B8 (without A1)	56	4	30*
Recurrent herpetic keratitis	B5	26	11	3
Cicatricial ocular pemphigoid	B12	45	20	3·2
Myasthenia gravis	HLA DRw3	32	17	2·3
	HLA B8	39	17	3·1
Thyrotoxicosis	HLA DW3	53	18	5·1
	HLA B8	44	18	3·6
Type I diabetes (juvenile)	HLA DRw3	27	17	1·8
	HLA DRw4	39	15	3·6
	HLA B8	32	16	2·5
Multiple sclerosis	HLA DRw2	41	22	2·5
	HLA Dw2	47	15	5
Ankylosing spondylitis	HLA B27	90	8	103·5
Reiter's disease	HLA B27	80	9	40·4
Rheumatoid arthritis	HLA DRw4	56	15	7·2
	HLA Dw4	60	12	11

*Normally B8 is in linkage disequilibrium with A1. Presence of B8 alone in juvenile diabetes increases the risk of retinopathy. Data on systemic diseases are from Bodmer and Bodmer (1978)

with a disease state is suspected, it is important to know the relative risk for normal persons in the general populations carrying the same antigen. This can be calculated with the help of the following simple formula:

Relative risk

$$= \frac{\text{HLA+ve patients}}{\text{HLA+ve control}} \times \frac{\text{HLA}-\text{ve control}}{\text{HLA}-\text{ve patients}}$$

Thus in ankylosing spondylitis, in which 90% of the patients are +ve for HLA B27 as compared to 8% in the control population, the relative risk is 103 (Table 2).

(*v*) Sometimes HLA association may not be obvious in those diseases where other modifying influences such as incomplete penetrance of the disease gene, varying exposure to external agents, or the presence of modifying genes may affect the expression of the disease. Sometimes genetic factors not connected with the HLA system may contribute to disease susceptibility. This, for example, may be operative in atopy, where genetic factors controlling the level of IgE interact with HLA-linked effects. It is also possible that the disease being studied is heterogeneous and the HLA association is only with a particular group of individuals having the disease. This is applicable to myasthenia gravis, where definite HLA association is found only in those patients who do not have thymoma.

HLA and eye disease

Following reports 6 years ago (Brewerton *et al.*, 1973a, 1973b) of a close association between HLA B27 and ankylosing spondylitis and acute anterior uveitis there has been almost a rush for the 'gold mine', and there is no dearth of reports in the ophthalmic literature incriminating an HLA antigen in a variety of ocular disorders of unknown aetiology (Tables 2 and 3). Some of the studies are based on logic and reasoning while others originate from sheer enthusiasm to explore new avenues. Consequently, the rules of statistics have been ignored by some and only partially obeyed by others. This has inevitably created chaos and has bewildered those who are desperately trying to keep up with this difficult and new concept of immunological modulation in a variety of histocompatibility-gene-related hereditary, degenerative, and inflammatory diseases of the eye. Unless the study is based on a large series

Table 3 *HLA and eye disease*

Disease	*Reference*	*Antigens tested*	*Observed increase in frequency*
Ocular cicatricial pemphigoid	Mondino *et al.*, 1978	A and B loci	A3, B12
Cogan's syndrome	Char *et al.*, 1975	A and B loci	B17
	Kaiser-Kupfer *et al.*, 1978	A and B loci	None
Keratoconus	Gasset *et al.*, 1977	A and B loci	B27 (only 3 patients studied)
Recurrent herpetic keratitis	Zimmerman *et al.*, 1977	A and B loci	B5
Primary open-angle glaucoma	Aviner *et al.*, 1976	A and B loci	Bw35
	Shin and Becker, 1977	A and B loci	B7, B12
	Grabner *et al.*, 1977	A, B, and C loci	None
	Damgaard *et al.*, 1978	A, B, and C loci	None
	Kass *et al.*, 1978	A and B loci	None
	Ritch *et al.*, 1978	A and B loci	None
	David *et al.*, 1979	A, B, and C loci	None
Pigment dispersion syndrome	Becker *et al.*, 1977	A and B loci	B13 and B17
	Kaiser-Kupfer and Mittal, 1978	A, B, and C loci	None
Acute anterior uveitis	Brewerton *et al.*, 1973	A and B loci	B27
	Ehlers *et al.*, 1974	A and B loci	B27
	Woodrow *et al.*, 1975	A and B loci	B27
Chronic iridocyclitis (adults)	Ohno *et al.*, 1977b	A and B loci	B27
Chronic iridocyclitis (juvenile)	Ohno *et al.*, 1977a	A and B loci	None
Behçet's disease	Ohno *et al.*, 1978	A and B loci	B5 (Japanese patients)
	Ohno *et al.*, 1978	A and B loci	B5 infrequent in American and British patients
	Jung *et al.*, 1976	A and B loci	
Vogt-Koyanagi-Harada syndrome	Tagawa *et al.*, 1977	A, B, and D loci	Bw54 and LD-wa (Both antigens are exclusive to Japanese)
Chorioretinitis	Bertrams *et al.*, 1978a	A and B loci	None
Toxoplasmic retinochoroiditis	Ohno *et al.*, 1977c	A and B loci	None
Malignant melanoma (choroid)	Bertrams *et al.*, 1978a	A and B loci	Aw32
Retinoblastoma	Bertrams *et al.*, 1973	A and B loci	Bw35
	Gallie *et al.*, 1977	A, B, and D loci	None
Eales's disease	Bertrams *et al.*, 1978a	A, B, and D loci	None
Presumed ocular histoplasmosis	Godfrey *et al.*, 1978	A, B, and D loci	B7
	Braley *et al.*, 1978	A, B, and D loci	B7
Diabetic retinopathy	Larkin *et al.*, 1978	A, B, and D loci	B8 (without A1) Juvenile-onset diabetes
	Moller *et al.*, 1978	A, B, C, and D loci	None (Adult-onset diabetes)
Central serous retinopathy	Bertram *et al.*, 1978a	A, B, C, and D loci	None
Haemorrhagic maculopathy	Flage *et al.*, 1977	A, B, and C loci	None
Rhegmatogenous retinal detachment	Bertrams *et al.*, 1978b	A, B, and C loci	B12
Retinitis pigmentosa (recessive)	Chen *et al.*, 1978	A, B, and C loci	None
Sjögren's syndrome	Chused *et al.*, 1977	A, B, and D loci	Dw3

and the results meet all the requirements of statistical significance already outlined, any report on HLA association and eye disease should be treated with reserve. Those who have patience and time should correct the P value if necessary, and calculate the relative risk, because although both of these statistical parameters are important they are often ignored by contributors to ophthalmic journals. Furthermore, it often pays to wait for independent confirmation of a reported finding.

Uveitis

The number of occasions when a specific aetiology of uveitis can be demonstrated or reasonably assumed is rarely more than about 50% and is frequently less, despite thorough investigations. Of all the arthritic conditions ankylosing spondylitis is the one most consistently associated with uveitis. It affects about a quarter of these patients, HLA B27 being present in 85 to 95% of patients with ankylosing spondylitis. In one study (Brewerton *et al.*, 1973a) 52% of 50 patients with anterior uveitis possessed B27, compared with 4% of the control group, and even in the absence of sacroiliitis 8 of 29 (28%) patients with acute anterior uveitis were B27 positive. The very close association of the disease with HLA B27 in Caucasian, Asian, and Japanese populations, suggests a disease susceptibility gene very closely linked to the HLA B locus. It is of interest that although the frequency of B27 is low in Negroes and ankylosing spondylitis may develop in the absence of this antigen, acute anterior uveitis in these B27-negative American Negroes is extremely rare (Khan *et al.*, 1977). Recent studies suggest that the frequency of HLA A2 is also increased in ankylosing spondylitis, but although there is associated increased frequency of HLA Cw1, Cw2, and Dw1 in B27-positive individuals, there is no difference in the distribution of these antigens in healthy persons and patients with ankylosing spondylitis (Sachs and Brewerton, 1978).

Uveitis with ulcers of the buccal mucosa and external genitalia form the triad of Behçet's disease, which is associated with several immunological changes, including the presence of immune complexes in patients' sera (Rahi *et al.*, 1976; Rahi *et al.*, 1979). Although the aetiology of the disease is still unknown, recent studies have shown that a large number of Japanese and Turkish patients possess HLA B5 antigen (Ohno *et al.*, 1978b); this, however, does not appear to be the case in Caucasian populations (Jung *et al.*, 1976; Ohno *et al.*, 1978a).

No HLA association has been found, however, in chronic anterior uveitis of childhood, choroidoretinitis and chronic cyclitis (Table 3).

The Vogt-Koyanagi-Harada syndrome is characterised by bilateral granulomatous uveitis in conjunction with variable degrees of skin and hair depigmentation, hair loss, and meningeal irritation. While the aetiology of this disease is obscure, evidence in favour of an autoimmune component is provided by the demonstration of antibodies to uveal pigment and cell-mediated allergy in the form of delayed skin hypersensitivity, lymphocyte transformation, and leucocyte migration inhibition. A close association with HLA Bw54 and LDwa (a Japanese D locus antigen) suggests the presence of uveitis susceptibility genes in the major histocompatibility system (Tagawa *et al.*, 1977).

Optic neuritis

Multiple sclerosis is much the most important cause of optic neuritis, and over half of the patients presenting with acute optic neuritis as an isolated sign later develop other features of multiple sclerosis. Although the aetiology of this disease is still unknown, and a virus infection is a strong possibility, it appears that multiple sclerosis is the only disease recognised to be strongly associated with HLA DRw2 and HLA Dw2 antigens in Caucasians. Recently, the syndrome of nephritis and lung haemorrhage (Goodpasture's syndrome), in which Bruch's membrane along with glomerular and other basement membranes is involved (Jampol *et al.*, 1975), in an antibody mediated type II reaction, has been shown to have the same association. Other HLA antigens, such as A3 and B7, also appear to be associated with optic neuritis. It has recently been shown that in patients with isolated optic neuritis the presence of BT101, which is closely related to HLA DRw2, is significantly associated with an increased risk of developing multiple sclerosis, especially in those individuals who develop ocular signs in the winter (Batchelor *et al.*, 1978).

Retinal diseases

Retinal involvement is a well-known complication of diabetes in which genetic, environmental, immunological, metabolic, and hormonal influences interact to produce the clinical picture of the disease. There is increasing evidence of a possible role of virus infection in the juvenile-onset (that is, type I) diabetes, which is often associated with islet cell and other organ-specific autoantibodies. Population studies have shown that there is an increased relative risk of developing type I diabetes in persons who are HLA Dw3 and DRw3 positive, with secondary association with HLA A1, B8, or B18, and in subjects who are Dw4 and DRw4 positive with secondary association with A2, B15, B40, and Cw3 (Cudworth and Festenstein, 1978). Owing to linkage disequilibrium HLA A1 is often associated with HLA B8, and therefore in only about 4% of the control population is B8 present in the absence of A1, as opposed to 56% of patients with juvenile diabetes with retinopathy. It has been concluded, therefore, that the presence of HLA B8 singly in patients with type I diabetes carries a bad prognosis (Larkins *et al.*, 1978). There is no evidence of HLA association, however, in retinopathy due to type II adult-onset diabetes (Moller *et al.*, 1978).

Studies on HLA association with a variety of other retinal diseases such as choroidoretinitis, toxoplasmic retinochoroiditis, Eales's disease, retinal detachment, haemorrhagic maculopathy, central serous retinopathy, and retinitis pigmentosa have been so far negative except in choroidoretinitis due to presumed histoplasmosis, in which increased frequency of HLA B7 has been reported (see Table 3 for references).

Glaucoma

The association of primary open-angle glaucoma with HLA antigens appears to be spurious, and although the increased incidence of antinuclear antibody in these patients is still controversial (Felberg *et al.*, 1977; Nagasubramanian *et al.*, 1978) recent reports from several countries (see Table 3) clearly show that there is no association between histocompatibility antigens and the propensity to develop a raised intraocular pressure with consequent loss of vision.

Intraocular tumours

The HLA system does not appear to exert any strong influence on the susceptibility of an individual to develop malignant disease. It is not surprising, therefore, that an earlier report of a possible HLA association with retinoblastoma (Bertrams *et al.*, 1973) has not been confirmed by other workers (Gallie *et al.*, 1977). There is some evidence, however, that malignant melanoma of the choroid may be associated with HLA Aw32, but this awaits confirmation.

Sjögren's syndrome

This condition predominates among women and in its fully developed form is characterised by keratoconjunctivitis sicca, xerostomia, and arthritis. Many patients have demonstrable rheumatoid factor in their sera, and Sjögren's syndrome specific (SS A and SS B) and non-specific antinuclear and antisalivary duct antibodies are also demonstrable in a proportion of these patients (Alspaugh *et al.*, 1976). The aetiology of Sjögren's syndrome is unknown, but a T-lymphocyte-mediated autoimmunity to a cellular component of salivary gland is strongly suspected. It is of interest, therefore, that increased frequency of HLA Dw3 has been reported in these patients (Chused *et al.*, 1977).

Myasthenia gravis

Ocular symptoms in myasthenia gravis include ophthalmoplegia, paresis of accommodation, inadequate convergence, and diplopia, though occasionally the disturbance may be limited to a degree of ptosis. Autoantibodies and T cell sensitisation to acetylcholine receptors are believed to play a pathogenetic role. About 30% of such patients show the presence of HLA B8 and HLA Dw3. It is of interest that HLA B8 is present in increased frequency in a number of autoimmune diseases, and it has been postulated that HLA B8 gene is closely concerned with T cell activity, especially suppressor T cell function, and this could account for the presence of several other unrelated autoantibodies in the sera of patients with myasthenia gravis.

Endocrine exophthalmos

At least half of thyrotoxic individuals develop signs of ocular involvement in the form of exophthalmos. The disease is often associated with a recently recognised autoantibody known as human specific thyroid stimulator; which, apart from stimulating the thyroid directly, facilitates binding of the exophthalmos-producing substance (a fragment of thyroid stimulating hormone) to the orbital tissues. As in other autoimmune disease there is a strong association between thyrotoxicosis and HLA B8 and HLA Dw3.

External disease of the eye

A high incidence of HLA A3 and B12 has been reported in ocular cicatricial pemphigoid (Mondino *et al.*, 1978), and HLA B5 is found in increased frequency in patients with recurrent herpetic keratitis. (Zimmerman *et al.*, 1977), but these claims await confirmation. Similarly, in a family study of keratoconus the mother and her 2 children were HLA B27 positive (Gassett *et al.*, 1977). It is of interest that a proportion of patients with keratoconus (which is a noninflammatory disease) are atopic and produce high levels of IgE (Rahi *et al.*, 1977). A high incidence of HLA B17 has been reported in Cogan's syndrome (Char *et al.*, 1975), but a recent report has failed to confirm this claim (Kaiser-Kupfer *et al.*, 1978).

In conclusion it may be said that apart from acute anterior uveitis, optic neuritis, and certain other autoimmune diseases such as myasthenia gravis and thyrotoxicosis, in which the eye is invariably involved, there is very little evidence of HLA association with other diseases of the eye. It is important not to be overenthusiastic about an apparently complex association with different antigens in studies based on a limited number of cases. Furthermore, strong positive association with one HLA antigen will necessarily entail negative association with other antigens, which may lead us to believe that the latter play a protective role. Such negative associations are difficult to establish, although one has been claimed for glaucoma (Shin and Becker, 1977), because the frequency of most antigens is already low and a further decrease is often unlikely to be judged as significant. Finally, so far, none of the HLA associations with disease is absolute. Even in the case of ankylosing spondylitis, although over 90% of persons with the disease may be positive for HLA B27, only a relatively small proportion of the population with B27 ever suffer from the disease.

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HLA antigens in glaucoma and ocular hypertension

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SUMMARY Forty-five white patients (32 with open-angle glaucoma and 13 with ocular hypertension) and 63 black patients (41 with open-angle glaucoma and 22 with ocular hypertension) were tissue typed for a total of 38 HLA antigens and the results compared to normal, unrelated, panels of 248 white donors and 150 black volunteers, respectively. No statistically significant differences with regard to the frequencies of 38 HLA antigens were detected among the various groups.

It is now generally accepted that genetic factors are involved to a considerable extent in the pathogenesis of primary open-angle glaucoma (OAG). An increased incidence of the disease has been reported among sibs and offspring of patients with glaucoma (Miller and Paterson, 1962; Leighton, 1968; Jay and Paterson, 1972). Furthermore, some of the features found in patients with glaucoma have been shown to be heritable, such as the cup/disc ratio (Armaly, 1967a), the hypersensitivity to topically administered corticosteroids (Armaly, 1967a, b) and the level of the intraocular pressure (Armaly, 1967c). While the exact mode of transmission in primary OAG has not been fully elucidated, evidence at present suggests a multifactorial mode of inheritance (Armaly, 1965; Jay and Paterson, 1972).

With the development of tissue typing, and the identification of the various HLA antigens, correlations have been found between some eye diseases and the increase in the frequency of certain HLA antigens in the affected population (Brewerton *et al.*, 1973; Brewerton *et al.*, 1974).

With evidence that certain features in OAG are genetically determined search for an association between HLA antigens and the disease has been undertaken. The results, however, are rather conflicting. Aviner *et al.* (1976) found an increased incidence of HLA Bw35 among their 49 patients with OAG, while Shin and Becker (1977) reported the opposite, the presence of HLA Bw35 apparently providing protection from glaucoma. In another study by the same group primary OAG was found to be associated with an increased incidence both of HLA B7 and of HLA B12 (Shin *et al.*, 1977), while Grabner and Mayr (1977) found no correlation between OAG and an increased or decreased frequency of any particular HLA antigen.

In the present study we report on our results of HLA typing in white and black patients with glaucoma and ocular hypertension.

Definition of criteria

Primary open-angle glaucoma: patients with glaucomatous visual field defects, excavation with atrophy of their optic disc in the presence of an intraocular pressure of 21 mmHg or more, and an open filtration angle.

Ocular hypertension: patients with intraocular pressure of 21 mmHg or more when tested repeatedly, a normal optic disc, no glaucomatous visual field defect, and an open filtration angle.

Patients and methods

One hundred and eight patients were included in the study. There were 45 white patients, 32 with OAG and 13 with ocular hypertension, and 63 black patients, 41 with OAG and 22 with ocular hypertension. All patients attended the Glaucoma Clinics at the Johannesburg General Hospital and St John's Eye Hospital, Baragwanath. The control panel consisted of 248 healthy, unrelated white donors and 150 unrelated black volunteers belonging to various Southern African tribes.

Tissue typing was performed at the Tissue Bank of the South African Institute for Medical Research. The method used was the Standard 2 Stage NIH

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Lymphocyte Microcytotoxicity Test at an incubation temperature of 37°C throughout the test and trypan blue as the indicator dye. A total of 174 different typing sera were used to identify 38 HLA antigens: 17 of the A locus, 18 of the B locus, and 3 of the C locus.

The statistical analysis of the results was performed by χ^2 test with Yates's correction. The P values obtained were corrected by multiplication with the number of antigens tested, Pc.

Results

The distribution of the frequencies of the various HLA antigens in the two races differ widely (Payne *et al.*, 1977). Therefore the 2 race groups in this study were dealt with separately. The frequencies of the 38 HLA antigens investigated in the glaucoma patients and ocular hypertensives as compared to the controls are presented in Tables 1 and 2 for the white groups and in Tables 3 and 4 for the black groups.

Table 1 *HLA antigen frequencies in white patients with glaucoma*

	Controls N=248 %	*OAG patients N=32 %*	χ^2y	*P*	*Pc*
HLA A1	27·0	25·0	0·001	NS	
Aw36	0·0	0·0			
A2	38·3	50·0	1·17	NS	
A3	31·5	12·5	4·04	<0·05	NS
A9	28·2	31·3	0·02	NS	
A10	3·2	3·1	0·25	NS	
Aw25	2·4	0·0	0·06	NS	
Aw26	4·8	15·6	4·05	<0·05	NS
Aw34	0·8	0·0	0·37	NS	
A11	12·1	6·3	0·47	NS	
A28	9·3	9·4	0·09	NS	
A29	7·2[1]	3·1	0·10	NS	
Aw30	1·8[1]	3·1	0·12	NS	
Aw31	9·1[1]	3·1	0·38	NS	
Aw32	5·5[1]	0·0	0·54	NS	
Aw33	1·8[1]	9·4	1·19	NS	
Aw43	0·0	0·0			
HLA B5	12·1	9·3	0·03	NS	
B7	29·0	18·8	1·02	NS	
Bw42	0·0	0·0			
B8	18·1	25·0	0·48	NS	
Bw16	8·9	15·6	0·81	NS	
B12	29·4	28·1	0·003	NS	
B37	1·6	6·3	1·12	NS	
B13	6·5	6·3	0·12	NS	
Bw35	17·3	21·9	0·15	NS	
B15	11·7	6·3	0·39	NS	
B18	4·0	3·1	0·06	NS	
B14	8·9	9·4	0·06	NS	
Bw21	3·2	3·1	0·25	NS	
Bw22	4·8	6·3	0·01	NS	
B27	9·7	3·1	0·80	NS	
B40	12·1	12·5	0·05	NS	
Bw41	0·0[2]	6·3	1·46	NS	
B17	14·1	9·4	0·21	NS	
HLA Cw2	5·0[2]	3·1	0·01	NS	
Cw3	18·3[2]	28·1	0·67	NS	
Cw4	20·0[2]	18·8	0·02	NS	
HLA B7 or B12	51·2	46·9	0·07	NS	
HLA A11 or Bw35	39·5	43·8	0·07	NS	

[1] Tested 55. [2] Tested 60.

Table 2 *HLA antigen frequencies in white patients with ocular hypertension*

	Controls N=248 %	*OHT patients N=13 %*	χ^2y	*P*	*Pc*
HLA A1	27·0	38·5	0·34	NS	
Aw36	0·0	0·0			
A2	38·3	30·8	0·06	NS	
A3	31·5	30·8	0·07	NS	
A9	28·2	15·4	0·48	NS	
A10	3·2	0·0	0·03	NS	
Aw25	2·4	7·7	0·07	NS	
Aw26	4·8	0·0	0·02	NS	
Aw34	0·8	0·0	1·71	NS	
A11	12·1	15·4	0·01	NS	
A28	9·3	15·4	0·06	NS	
A29	7·2[1]	7·7	0·29	NS	
Aw30	1·8[1]	0·0	0·63	NS	
Aw31	9·1[1]	0·0	0·29	NS	
Aw32	5·5[1]	7·7	0·12	NS	
Aw33	1·8[1]	0·0	0·63	NS	
Aw43	0·0	0·0			
HLA B5	12·1	7·7	0·002	NS	
B7	29·0	23·0	0·02	NS	
Bw42	0·0	0·0			
B8	18·1	23·0	0·01	NS	
Bw16	8·9	0·0	0·37	NS	
B12	29·4	15·4	0·60	NS	
B37	1·6	7·7	0·27	NS	
B13	6·5	0·0	0·12	NS	
Bw35	17·3	15·4	0·04	NS	
B15	11·7	7·7	0·00	NS	
B18	4·0	7·7	0·005	NS	
B14	8·9	23·0	1·47	NS	
Bw21	3 2	23·0	7·64	<0·01	NS
Bw22	4·8	7·7	0·04	NS	
B27	9·7	0·0	0·47	NS	
B40	12·1	7·7	0·0	NS	
Bw41	0·0[2]	0·0			
B17	14·1	0·0	1·08	NS	
HLA Cw2	5·0[2]	7·7	0·08	NS	
Cw3	18·3[2]	15·4	0·02	NS	
Cw4	20·0[2]	0·0	1·82	NS	

[1] Tested 55. [2] Tested 60.

WHITE GROUPS

In the white glaucoma group a decrease of the frequency of A3 and an increase in the frequency of Aw26 was found (see Table 1). These values did not reach statistical significance when P was corrected.

An increased incidence of the antigens Bw21 and Cw2 were noted in white ocular hypertensives (see Table 2). These results, however, are most probably attributable to the small number of patients in this group and were no longer statistically significant when P was corrected.

Table 3 *HLA antigen frequencies in black patients with glaucoma*

	Controls N=150 %	*OAG patients N=41* %	$\chi^2 y$	*P*	*Pc*
HLA A1	6·0	4·9	0·01	NS	
Aw36	0·0	0·0			
A2	25·3	22·0	0·06	NS	
A3	12·0	9·8	0·02	NS	
A9	17·3	19·5	0·01	NS	
A10	0·7	2·4	0·02	NS	
Aw25	0·0	0·0			
Aw26	15·3	19·5	0·16	NS	
Aw34	7·3	9·8	0·03	NS	
A11	0·7	0·0	0·49	NS	
A28	22·7	17·1	0·31	NS	
A29	11·3	14·6	0·09	NS	
Aw30	28·7	39·0	1·17	NS	
Aw31	16·0	4·9	2·51	NS	
Aw32	2·7	4·9	0·05	NS	
Aw33	2·0	0·0	0·04	NS	
Aw43	2·7	2·4	0·19	NS	
HLA B5	4·7	4·9	0·13	NS	
B7	18·7	17·1	0·00	NS	
Bw42	19·3	12·2	0·69	NS	
B8	8·7	9·8	0·01	NS	
Bw16	2·0	7·3	1·50	NS	
B12	24·0	26·9	0·03	NS	
B37	0·0	0·0			
B13	1·3	2·4	0·04	NS	
Bw35	10·7	14·6	0·18	NS	
B15	2·7	2·4	0·22	NS	
B18	13·3	7·3	0·61	NS	
B14	5·3	2·4	0·13	NS	
Bw21	0·7	0·0	0·49	NS	
Bw22	3 3	4·9	0·00	NS	
B27	0·7	0·0	0·49	NS	
B40	2·0	0·0	0·04	NS	
Bw41	10·3	2·4	0·04	NS	
B17	34·7	39·0	0·11	NS	
HLA Cw2	36·7	26·8	0·98	NS	
Cw3	20·0	4·9	4·25	$<0·05$	NS
Cw4	22·7	46·3	7·86	$<0·01$	NS
HLA B7 or B12	41·3	43·9	0·01	NS	
HLA A1 or A11	6·7	4·9	0·00	NS	

BLACK GROUPS

Cw3 showed a decreased frequency and Cw4 an increased frequency in the black glaucoma patients, but again when P was corrected no statistical significance resulted (see Table 3). There was no deviation from the normal HLA antigen distribution in the black ocular hypertensives (Table 4).

Discussion

The results in this series are in accordance with the findings of Grabner and Mayr (1977), who found no difference in the incidence of any of the 36 HLA antigens tested in their 41 white patients with OAG when compared to 450 controls. Their and our results, however, are in discordance with reports which found associations (positive and negative) between certain HLA antigens and glaucoma. Shin *et al.* (1977) and Shin and Becker (1976) found a highly significant association between the B locus antigens B7 and B12 in both their white and black patients with OAG. The significance increased further when the presence of either 1 of the 2 antigens was considered. In our series these 2 antigens were not found to be present more frequently in patients with OAG, white or black.

Becker and Shin (1977) observed also an increased prevalence of HLA A3 in their white but not in their black patients with OAG. This is to be expected, as HLA A3 and HLA B7 occur in a marked positive linkage disequilibrium in the white population but not in the black (Payne *et al.*, 1977; Hammond *et al.*, 1977). Therefore an increase in the frequency of HLA B7 in the white group would probably be accompanied by a concomitant increase in HLA A3. Far more importance could be attached to an increase in HLA A3 if it should occur in a group of black patients.

Table 4 *HLA antigen frequencies in black patients with ocular hypertension*

	Controls N=150 %	*OHT patients N=22* %	$\chi^2 y$	*P*	*Pc*
HLA A1	6·0	4·5	0·05	NS	
Aw36	0·0	0·0			
A2	25·3	18·2	0·21	NS	
A3	12·0	9·1	0·00	NS	
A9	17·3	9·1	0·45	NS	
A10	0·7	0·0	1·25	NS	
Aw25	0·0	0·0			
Aw26	15·3	13·6	0·01	NS	
Aw34	7·3	9·1	0·02	NS	
A11	0·7	0·0	1·25	NS	
A28	22·7	27·3	0·04	NS	
A29	11·3	27·3	2·94	NS	
Aw30	28·7	22·7	0·11	NS	
Aw31	16·0	9·1	0·28	NS	
Aw32	2·7	0·0	0·00	NS	
Aw33	2·0	4·5	0·00	NS	
Aw43	2·7	0·0	0·04	NS	
HLA B5	4·7	4·5	0·27	NS	
B7	18·7	18·2	0·06	NS	
Bw42	19·3	13·6	0·12	NS	
B8	8·7	4·5	0·06	NS	
Bw16	2·0	0·0	0·04	NS	
B12	24·0	31·8	0·28	NS	
B37	0·0	0·0			
B13	1·3	0·0	0·27	NS	
Bw35	10·7	13·6	0·00	NS	
B15	2·7	0·0	0·00	NS	
B18	13·3	9·1	0·05	NS	
B14	5·3	0·0	0·32	NS	
Bw21	0·7	0·0	1·25	NS	
Bw22	3·3	4·5	0·11	NS	
B27	0·7	0·9	1·25	NS	
B40	2·0	0·0	0·04	NS	
Bw41	1·3	0·0	0·27	NS	
B17	34·7	54·5	2·45	NS	
HLA Cw2	36·7	36·4	0·04	NS	
Cw3	20·0	18·2	0·01	NS	
Cw4	22·7	36·4	1·28	NS	

Furthermore, confusion exists with regard to the association of Bw35 and OAG. Aviner *et al.* (1976) found an increased incidence of HLA Bw35 in a group of patients with OAG, whereas Shin and Becker (1977) and Becker and Shin (1977) found that this antigen provides protection from OAG in whites. Our findings confirm the results of Grabner and Mayr (1977), who were unable to find a relationship between the antigen Bw35 and OAG. The observation of Aviner *et al.* (1976) should be interpreted with reserve, as they compared a racially mixed group of patients with an exclusively Caucasian control panel.

The decrease in the antigen HLA A11 in both white and black patients with glaucoma, and hence the assumed protection afforded by this antigen as stated by Shin and Becker (1977) and Becker and Shin (1977), was not borne out by our results. In the white patients this can be partly attributed to the difference in the control groups. Our controls were unselected, whereas those of Shin and Becker were preselected corticosteroid nonresponders and had a frequency of HLA A11 much higher than one would expect from a random white panel (Payne *et al.*, 1977). In addition the reported low incidence of HLA A11 (Becker and Shin, 1977) in their black patients is in fact the figure one would expect in any normal black population, HLA A11 being an extremely rare antigen in negroid people (Ward and Biegel, 1976; Hammond *et al.*, 1977; Payne *et al.*, 1977). The unusually high frequency of HLA A11 in their black controls was established from the extremely small number of 28 controls.

The only related patients in our series were 2 HLA identical sisters. Their antigen typing was as follows: HLA A2-B12, w22. One of the patients has advanced primary OAG while the sister is an ocular hypertensive followed up untreated for more than 8 years.

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Immunoglobulin concentrations in human tears in ocular diseases

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SUMMARY Immunoglobulin concentrations in human tears were determined in 165 patients with different eye diseases by a standard radial immunodiffusion method. IgA was present in all the samples in measurable quantity. The mean IgA values were significantly higher than the controls in patients with acute bacterial conjunctivitis, keratomalacia, corneal graft reaction, blepharoconjunctivitis, and acute keratoconjunctivitis. The values in the patients with vernal conjunctivitis, phlyctenular conjunctivitis, acute bacterial corneal ulcer, and acute endogenous uveitis were not significantly different from those in the controls. IgG could be detected in the majority of the samples but it was in measurable quantity in 18 samples. IgM could be detected in fewer samples. IgD was not detected in any of them. The study indicates that, whenever the immunoglobulin levels in tears are altered in diseased eyes, it is the IgA level that is predominantly altered and not the IgG level.

The immunoglobulin found predominantly in fluids coating mucous membrane surfaces such as the conjunctiva, respiratory tract, and gastrointestinal tract may be important local agents of a defence mechanism in initial or recurrent bacterial or other infectious processes (Little *et al.*, 1969). Several reports (Smith *et al.*, 1967; Douglas *et al.*, 1967; Waldman *et al.*, 1968) suggest that immunoglobulin A in parotid, nasal, and throat secretions plays a role in local immunity to respiratory infection. The host defence mechanism has also been detected in lacrimal and conjunctival secretions, where local humoral immunity appears to be important (Centifanto and Kaufman, 1970). An earlier study by the present authors has established the immunoglobulin levels in tears of normal Indian people (Sen *et al.*, 1976, 1978). The purpose of the present study was to see whether there is any appreciable change in the immunoglobulin concentrations in tears in patients suffering from various ocular diseases.

Patients and methods

The study was carried out among 220 healthy people and 165 patients with different eye diseases chosen consecutively from the Eye Outpatient Department of Irwin Hospital, New Delhi. The former group comprised people who had no evidence of ocular or systemic disease and who had attended mainly for refraction. There were 111 males and 109 females in the healthy group, and their ages ranged from 2 to 86 years. A detailed analysis of data on tear immunoglobulin levels of this healthy group has been reported earlier (Sen *et al.*, 1978).

The patients were grouped into 3 categories according to whether they had conjunctival, corneal, or miscellaneous diseases. The number of cases in each clinical subgroup, their sex distribution, and age range are given in Table 1. The diagnosis was established by detailed clinical examination, including slit-lamp biomicroscopy, direct and indirect ophthalmoscopy, and relevant laboratory investigations.

Tear specimens were collected by the method already described (Sen *et al.*, 1976). They were stored at –20°C until needed. IgA, IgG, IgM, and IgD were quantified by the single radial immunodiffusion technique (Mancini *et al.*, 1965). Monospecific goat antisera against heavy chain human IgA, IgG, IgM, and IgD and the respective reference standards except that of IgA were obtained from Meloy Laboratories, Virginia, USA. The reference standard of secretory IgA, purified from human colostrum, was used. The concentrations of immunoglobulins were calculcated from the calibration curve

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Table 1 *Age-sex distribution of patients and their tear IgA levels compared to matched controls*

Clinical conditions	*No. of cases*	*Males*	*Females*	*Age range in years*	*Size of matched control group*	*IgA in mg/100 ml*			
						Clinical conditions		*Matched control*	
						Mean ± SD	*CV (%)*	*Mean ± SD*	*CV (%)*
Group A									
Acute bacterial conjunctivitis	40	23	17	5–55	90	33·9±18·8	55·4	26·0±13·2	50·7
Phlyctenular conjunctivitis	22	13	9	7–20	60	23·0±14·0	60·8	25·8±12·9	50·0
Vernal conjunctivitis	10	4	6	7–40	40	33·5±20·9	62·3	26·5±15·1	56·9
Group B									
Keratomalacia	14	6	8	4–12	30	54·2±29·5	54·4	26·3±13·6	51·7
Corneal graft reaction	6	6	0	26–52	36	41·8±17·5	41·8	28·0±16·4	58·5
Acute bacterial corneal ulcer	15	6	9	6–75	42	20·4±19·6	96·0	28·8±20·2	70·1
Group C									
Blepharoconjunctivitis	11	6	5	10–45	45	68·2±34·2	50·1	30·0±15·9	53·0
Acute keratoconjunctivitis	16	4	12	11–54	45	47·7±28·5	59·7	27·4±15·2	55·4
Acute endogenous uveitis	31	22	9	14–65	31	28·5±15·1	52·9	31·4±17·3	55·0

constructed by incorporating 3 known concentrations of standard for every set of immunoglobulin determinations. The lower level of sensitivity of the plates was 1 mg/100 ml.

It had been found in our earlier study among normal people that the IgA level varied according to age and sex (Sen *et al.*, 1978). Thus a direct comparison would have been invalid, since the various clinical subgroups differed considerably from the healthy group in their age-sex distribution. Therefore, to ensure the validity of the conclusions, random samples were drawn from the healthy group to match the clinical subgroup in respect of its size and age-sex composition for comparing the IgA values.

Results

IgA was present in all the tear samples in measurable quantity. The mean, standard deviation, and coefficient of variation (CV) of IgA values obtained in different clinical subgroups and the respective matched control groups are given in Table 1.

In group *A* only patients in the subgroup acute bacterial conjunctivitis were found to have a significantly higher mean IgA level than the matched controls (t = 2·52 for 128 df, P<0·02). The values in the case of phlyctenular conjunctivitis were not significantly different from the matched controls (t = 0·85 for 80 df, P>0·3). The apparently high mean value in cases of vernal conjunctivitis did not attain statistical significance (t = 1·21 for 48 df, P>0·2). In group *B* patients with keratomalacia (t = 4·04 for 42 df, P<0·001) and corneal graft reaction (t = 2·04 for 40 df, P<0·05) were found to have mean IgA levels significantly higher than the matched controls. Patients with acute bacterial corneal ulcer had a lower value than matched controls, but the difference did not attain statistical significance (t = 1·53 for 55 df, 0·1<P<0·2). In group *C* patients with blepharoconjunctivitis and acute keratoconjunctivitis were found to have a significantly higher mean IgA levels (t = 4·46 for 54 df, P<0·001, and t = 2·58 for 59 df, P<0·01) than the respective matched controls, whereas those with acute endogenous uveitis were not significantly different from the matched control (t = 0·70 for 60 df, P>0·40).

IgG could be detected in 137 samples, but it was measurable in only 18 samples (Table 2). IgM could be detected in 23 samples but could be measured in 7 (Table 3). IgD was not detected in any of them. In the healthy group of 220 people IgG was detected in 200 and IgM in only 7 samples. In all those samples positive for IgG and IgM the immunoglobulin was present only in trace amounts (<1 mg/100 ml). IgD was not detected in any sample.

Discussion

Several studies have been reported on immunoglobulin levels in tears of normal persons (Chodirker and Tomasi, 1963; Barnett, 1968; Josephson and Weiner, 1968; Little *et al.*, 1969; Knopf *et al.*, 1970;

Table 2 *Tear IgG in mg/100 ml in various eye diseases*

Clinical conditions	*No. of cases*	*No. of cases where not detectable*	*No. of cases with trace amounts*	*Present in measurable quantity*	
				No. of cases	*Range*
Group A					
Acute bacterial conjunctivitis	40	7	28	5	3·5–11·5
Phlyctenular conjunctivitis	22	2	19	1	1·9
Vernal conjunctivitis	10	2	7	1	5·9
Group B					
Keratomalacia	14	3	11	0	—
Corneal graft reaction	6	0	4	2	3·3 and 6·2
Acute bacterial corneal ulcer	15	3	10	2	2·9 and 3·5
Group C					
Blepharoconjunctivitis	11	4	5	2	4·5 and 19·6
Acute keratoconjunctivitis	16	4	9	3	11·8–16·0
Acute endogenous uveitis	31	3	26	2	3·9 and 8·0

Table 3 *Tear IgM in mg/100 ml in various eye diseases*

Clinical conditions	*No. of cases*	*No. of cases where not detectable*	*No. of cases with trace amounts*	*Present in measurable quantity*	
				No. of cases	*Range*
Group A					
Acute bacterial conjunctivitis	40	32	5	3	6·5–9·5
Phlyctenular conjunctivitis	22	19	2	1	7·3
Vernal conjunctivitis	10	10	0	0	—
Group B					
Keratomalacia	14	11	1	2	3·7 and 5·8
Corneal graft reaction	6	5	1	0	—
Acute bacterial corneal ulcer	15	13	2	0	—
Group C					
Blepharoconjunctivitis	11	10	1	0	—
Acute keratoconjunctivitis	16	14	2	0	—
Acute endogenous uveitis	31	28	2	1	4·3

Brauninger and Centifanto, 1971; Sen *et al.*, 1976), but there is little information on the level of immunoglobulin concentrations in tears in diseased eyes. In the few published reports the numbers of cases studied were small. Bluestone *et al.* (1975) studied a few cases with miscellaneous eye diseases and found only the IgA level rising in the tears. Chandler *et al.* (1974), on the other hand, found the IgA level remaining remarkably constant despite the presence of disease and the IgG level rising in such conditions. McClellan *et al.* (1973) also found the IgG level rising in diseases of the external eye and thought the rise was probably due to transudation of serum proteins into the tears. However, the present study indicates that whenever there is alteration in the level of immunoglobulins in tears in the diseased eyes it is the level of IgA that is predominantly altered.

The level of IgA was significantly raised in acute bacterial conjunctivitis, blepharoconjunctivitis, acute keratoconjunctivitis, keratomalacia, and corneal graft reaction. In cases of protein-calorie malnutrition serum immunogloblulins and those in external secretions are expected to be low. However, an increase of tear IgA level in keratomalacia can be explained on the basis of repeated infection that occurs at the site in such cases. Mata and Faulk (1973) reported an increase of serum IgA values in protein-calorie malnutrition, and this has been attributed to repeated antigenic stimulation via the respiratory and gastrointestinal tracts (Sirisinha *et al.*, 1975). It is interesting to note that cases of acute bacterial corneal ulcer had a lower IgA level than the controls. However, further study would be needed to determine whether or not a state of local deficiency of IgA exists in such cases. It is of interest that secretory IgA in tears is remarkably low in patients with ocular complications following treatment with beta-blockers (Garner and Rahi, 1976).

In phlyctenular conjunctivitis and acute endogenous uveitis the stimulation is systemic and therefore no rise in the IgA level in tears was expected. However, there was also no appreciable change in the values of the immunoglobulins in vernal conjunctivitis, in which the stimulation is at the local site.

In most of the cases with a higher level of IgA in tears there was no corresponding rise in the level of IgG. This suggests increased local production of IgA as a result of stimulation at the site, for leakage of serum into the tears would have substantially raised the level of IgG. Our findings of generally low IgG level in the tear samples from diseased eyes are in agreement with Bluestone *et al.* (1975), who found IgG usually detectable but occasionally quantifiable even in tears from diseased eyes.

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Cell mediated immunity in relation to cataract and cataract surgery

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SUMMARY Two groups of patients suffering from cataract were investigated by the lymphocyte stimulation test. One group was tested before and the other after cataract surgery. Human (total) lens crystallins and bovine alpha crystallin were used as the antigens. Lymphocytes of healthy persons showed practically no positive stimulation with either antigen. Of the patients tested before operation 38% reacted positively with lens crystallins and 15% with alpha crystallin. This difference in sensitisation suggests a leakage of lenticular antigens other than alpha crystallin out of the lens during cataract progression. Extracapsular lens extraction caused an increase in the number of patients reacting positively with lens crystallins and alpha crystallin as compared to patients not operated upon. Intracapsular lens extraction on the other hand resulted in less sensitisation to lens crystallins as compared to patients not operated upon.

The isolation of the lens proteins from the fetal circulation early in embryonic life, the lack of innervation, and the complete avascularity of the adult lens might suggest that the lens proteins initiate an autologous sensitisation after entering the aqueous humour. However, it has only recently been possible to detect antibodies to homologous lens proteins in small amounts in rabbits (Misra *et al.*, 1977). Earlier attempts to stimulate anti-lens antibody formation were successful only by sensitisation with homologous lens proteins in combination with an adjuvant (Halbert *et al.*, 1965). The presence of an adjuvant still seems necessary for the immune response to autologous lens antigens (Rahi *et al.*, 1977).

Phacogenic uveitis or lens-induced uveitis, which is characterised by a sterile iridocyclitis, is thought to be the result of autosensitisation to lens proteins. Clinically this inflammation may develop within 2 days after perforation of the lens capsule (Schlaegel, 1975), indicating a secondary immune response. The primary response of the immune system could have been evoked by leakage of lenticular antigen into the aqueous humour during cataract maturation. Because it is difficult to induce a good antibody response after immunisation with homologous or autologous lens proteins it is likely that cellular immunity plays a role in the induction of phacogenic uveitis.

The present study deals with the *in-vitro* stimulation by lens crystallins and alpha crystallin of lymphocytes of patients suffering from cataract in order to investigate this possible leakage. In addition, a comparison of lymphocyte activation has been made before and after cataract surgery.

Patients and methods

The investigation covered 49 patients suffering from cataract, who were divided into 2 groups. The first group consisted of 21 patients who were tested 1 day before cataract surgery and who had not been operated on before. The second group consisted of 28 patients who were tested at least 18 days after cataract surgery. Patients who received corticosteroid or other anti-inflammatory preparations during the investigation were excluded. Twenty-two healthy volunteers (age range 20 to 64 years, including 8 persons between 51 and 64 years) served as controls. Two of them could not be tested with alpha crystallin.

PREPARATION OF ANTIGENS

Cataractous lenses (age range of patients 60 to 70 years) removed after intracapsular lens extraction were used after storage at −70°C. Lens crystallins were isolated by homogenisation of the decapsulated lenses in excess 0·01 M ammonium acetate buffer (pH 7·2) in a Potter-Elvehjem tube at 4°C. The

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suspension was centrifuged for 1 hour at 15 000 *g* at 4°C and the supernatant was lyophilised and stored at –20°C until used. Protein content of the dry weight material (lens crystallins) was determined by the Lowry method (Lowry *et al.*, 1951) and amounted to 80%. Serum albumin was used as standard.

Alpha crystallin, the non-species-specific lens crystallin (Halbert *et al.*, 1965), was isolated from fresh decapsulated bovine lenses as follows. Bovine lens crystallins were isolated as from human lenses; 80 mg of bovine lens crystallins were dissolved in 5 ml 0·1 M ammonium acetate buffer (pH 8·0) supplemented with 0·5% butanol and applied to a Sepharose 6B column (100 × 2·5 mm) (Bours and Brahma, 1973). The column was eluted with the same buffer. The fractions containing pure alpha crystallin (as checked by isoelectrofocusing) (Bours and Brahma, 1973) were lyophilised and stored at –20°C until used.

LYMPHOCYTE STIMULATION ASSAY (LSA)

Heparinised blood was diluted with an equal volume of Eagle's minimum essential medium (MEM). The mononuclear cells were isolated from the diluted blood by Ficoll-Isopaque centrifugation (Du Bois *et al.*, 1973). Lymphocytes, 3×10^5, were suspended in 1 ml MEM supplemented with 100 units of penicillin and 0·1 mg of streptomycin per millilitre and 20% heat-inactivated A-rh positive serum. Cultures of lymphocytes were incubated in triplicate with 1 mg human lens crystallins or 50 μg bovine alpha crystallin for 6 to 7 days. Viability and stimulation activity was checked by incubating the lymphocytes with 5 μg phytohaemagglutinin-P (Difco) for 3 days. Control cultures contained neither antigen nor mitogen. Sterility was controlled by incubating the antigens alone in the culture medium. Twenty-four hours before harvesting, 0·5 μCi tritiated thymidine (specific activity 25 curi/millimole) was added. Harvesting of the cells was done by filtration under reduced pressure through Millipore glassfibre filters. The filters were incubated in 0·5-ml Nuclear Chicago Solubilizer (NCS), diluted 1 to 3 with toluene-based scintillation fluid containing 100 mg dimethyl-POPOP* and 5 g PPO†/litre for 30 minutes at 20°C. After addition of 9·5 ml scintillation fluid containing 1 ml glacial acetic acid per litre the activity was determined in a liquid scintillation counter. The degree of stimulation was expressed as the stimulation index (SI). SI = counts per minute (cpm) in the presence of antigen divided by cpm in the absence of antigen. An SI $\geqslant 3$ with human lens crystallins and an SI $\geqslant 2$ with bovine alpha crystallin was considered to be positive.

Results

LSA BEFORE CATARACT SURGERY

Lymphocytes from 21 patients, obtained 1 day before cataract surgery, were cultured with total lens crystallins and alpha crystallin. Eight (38%) of these patients showed a positive lymphocyte response with total lens crystallins (Table 1, Fig. 1). Two healthy persons (9%) showed a positive lymphocyte stimulation with lens crystallins (persons aged 34 and 64 years) (Fig. 1). The difference in total lens crystallins sensitisation between healthy persons and cataract patients was statistically significant ($P < 0·05$; Fisher's one-sided exact test). Alpha crystallin produced a positive lymphocyte culture in 3 (15%) of the 20 patients investigated (Table 1, Fig. 1), which was statistically insignificant in comparison with the group of 20 healthy persons, who did not react with alpha crystallin ($P > 0·1$) (Fig. 1). In addition to 5 patients with a mature cataract 14 patients suffered from a cataract in which the lens cortex was involved, and 8 patients

Table 1 *Stimulation of lymphocytes of patients, suffering from cataract, before cataract surgery*

Case	Sex	Age (yr)	*Cataract type* Nuclear	Cortical	Other	*Stimulation index with* Lens crystallins*	Alpha crystallin†
1	M	77		+		–	–
2	M	58			Mature	–	–
3	M	63	+	+		–	–
4	F	39			Mature	–	–
5	M	38		+		+	+
6	M	42		+		–	–
7	F	78	+	+		–	–
8	M	75		+		–	–
9	M	57			Mature	+ +	–
10	M	66		+		+ +	–
11	M	66	+			–	–
12	F	71	+	+		+ +	–
13	M	64	+	+		–	–
14	M	53		+		–	–
15	M	64			Mature	+ + +	+ +
16	F	71			Mature	+ +	–
17	F	76	+	+		–	–
18	M	57		+		+ + +	+
19	M	79	+	+		+ + +	–
20	M	67		+		–	–
21	F	83	+			–	ND‡

* + = SI 3–5; + + = SI 5–7; + + + = SI > 7.
† + = SI 2–4; + + = SI 4–6.
‡ Not determined.

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*POPOP = 2,2-*p*-phenylen bis (5-phenyloxazol).
†PPO = 2,5-diphenyloxazol.

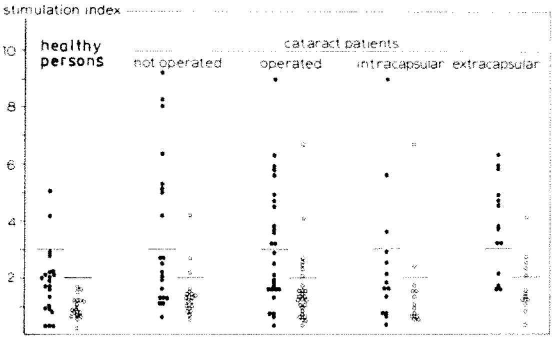

Fig. 1 *Stimulation of lymphocytes of healthy persons and cataract patients by total human lens crystallins (●) and bovine alpha crystallin (○). The influence of cataract surgery and type of lens extraction (intracapsular and extracapsular) are shown. An SI ⩾ 3 with total human lens crystallins and an SI ⩾ 2 with bovine alpha crystallin (horizontal bars) was considered to be positive*

Table 2 *Stimulation of lymphocytes of patients after cataract surgery*

			Stimulation index with		*Lens extraction*	
Case	*Sex*	*Age (yr)*	*Lens crystallins**	*Alpha crystallin†*	*Intra-capsular*	*Extra-capsular*
22	F	69	–	–	+	
23	M	28	+	+		+
24	M	39	+	–		+
25	F	69	–	–	+	
26	M	58	–	–	+	
27	F	63	–	–		+
28	M	78	–	–	+	
29	M	77	–	–		+
30	F	60	–	–		+
31	M	71	+	–		+
32	F	66	–	–	+	
33	F	65	+	–		+
34	M	73	+	–		+
35	F	86	–	–	+	
36	F	65	+ +	+		+
37	M	42	+ +	+		+
38	M	67	–	–	+	
39	M	66	+	+ +		+
40	F	78	+ +	+ + +	+	
41	F	80	+	+	+	
42	F	71	–	–		+
43	M	66	+	–		+
44	M	62	+ +	+		+
45	M	64	–	–	+	
46	M	82	–	–	+	
47	F	83	–	–	+	
48	F	71	+ + +	ND‡	+	
49	M	57	–	–	+	

* + = SI 3–5; + + = SI 5–7; + + + = SI > 7.
† + = SI 2–4; + + = SI 4–6; + + + = SI > 6.
‡ Not determined.

suffered from a cataract in which the lens nucleus was involved.

LSA AFTER CATARACT SURGERY

A positive stimulation index with total lens crystallins was found in 13 (46%) of the 28 patients who underwent cataract surgery (Table 2, Fig. 1), which is about the same percentage as before cataract surgery. Lens extraction produced a rise in the number of patients who reacted positively with alpha crystallin (Table 2, Fig. 1). Seven patients (26%) of the 27 were alpha crystallin sensitive after operation, which was significantly higher than in the group of healthy persons ($P < 0{\cdot}05$).

Table 2 and Fig. 1 also show the influence of the type of cataract extraction on the sensitisation to total lens crystallins and alpha crystallin. Of 14 patients who underwent intracapsular lens extraction 3 patients (21%) reacted positively with lens crystallins and 2 (15%) of the 13 tested patients reacted positively with alpha crystallin. These numbers were not significantly different from those of healthy persons ($P > 0{\cdot}1$ for both antigen fractions). However, of 14 patients who underwent extracapsular lens extraction 10 (71%) showed sensitisation to lens crystallins and 5 (35%) to alpha crystallin. This difference in alpha crystallin and lens crystallins sensitisation between patients who underwent extracapsular lens extraction and healthy persons was statistically significant ($P < 0{\cdot}01$ and $P < 0{\cdot}0005$, respectively).

Discussion

Differences have been found in protein content as well as in protein composition between normal and cataractous lenses. Declining lens transparency appears to be associated with a decrease in the quantity of soluble lens proteins and an increase in the amount of insoluble proteins (Mach, 1963). A preferential decrease in low molecular weight proteins during progressive cataract formation was found by Sephadex gel filtration (François *et al.*, 1965). Several authors suggested that these proteins are gamma crystallin (Maisel and Goodman, 1965; Croft, 1973). According to Harding and Dilley (1976) different explanations are possible for this decline in low molecular weight proteins in the lens, namely, by leakage through the lens capsule, by conversion into insoluble proteins, by cross-linking, or by a lack of synthesis. Mach (1963) has already demonstrated that the increase in protein insolubilisation cannot account for the decrease in quantity of soluble low molecular weight lens proteins during cataractogenesis. Charlton and van Heyningen (1968) considered the possibility of leakage of low molecular weight proteins out of the lens, but their results did not lead to definite conclusions.

If leakage of lenticular proteins does occur during opacification of the lens, an immune response could be provoked leading to a population of sensitised lymphocytes in the patients' blood. The present investigation supports this by showing that about 38% of the cataract patients (who had not been operated on before) had lymphocytes which could be stimulated by lens crystallins (Table 1). Normal persons showed practically no positive reactions with lens crystallins. Only 3 (15%) of the 20 patients investigated reacted positively with alpha crystallin (Table 1). One of these 3 patients suffered from a mature cataract and another patient suffered besides from cataract from recurrent uveitis. None of the control persons showed a positive response to alpha crystallin. As is shown in Table 1, most (66%) of the patients who had not been operated on before suffered from a cortical cataract in contrast to 38% of these patients with a nuclear cataract.

Philipson (1973) compared the morphological changes in both cortical and nuclear cataractous lenses by electron microscopy, microradiography, and light scattering. The cortical opacities appeared to be accompanied by an enlargement of intercellular spaces followed by lens membrane damage. The human nuclear cataract looked completely different. In this type of cataract lens fibre cells and membranes did not show any difference from those of normal lenses. The morphological changes commonly seen in cortical cataractous lenses may lead to selective permeability of the lens capsule, resulting in liberation of low molecular weight lens proteins, subsequently provoking an immunological response. The high percentage of patients with cortical cataract, present in the group of patients who had not been operated on before, strengthens the idea that leakage of the lenticular proteins depends on the condition of the lens cortex rather than the lens nucleus.

Cataract surgery seems to have little influence on the sensitisation of the lymphocytes to total lens crystallins. On the contrary, after cataract surgery an increase in the number of patients sensitive to alpha crystallin could be detected.

Separating the patients according to the type of cataract extraction showed that after extracapsular lens extraction 71% of the patients reacted positively with lens crystallins and 35% with alpha crystallin. Of patients who underwent intracapsular lens extraction, however, 21% showed a sensitisation to lens crystallins and 15% to alpha crystallin. This difference in sensitisation to lens crystallins and to alpha crystallin between both types of extraction procedures can be explained by the liberation of lens antigens into the aqueous humour, which is accomplished during extracapsular lens extraction. Intracapsular lens extraction results in a complete removal of the source of lens antigens. The latter also explains the lower percentage of patients showing sensitivity to lens crystallins after intracapsular lens extraction as compared to the patients not operated on.

The results suggest that lenticular proteins other than alpha crystallin are free to pass the lens capsule predominantly in cortical cataractous lenses. After entering the aqueous humour a primary immune response can be induced leading to a population of sensitised lymphocytes. This primary sensitisation possibly concerns a cell mediated response because: (*a*) Attempts to induce anti-lens antibodies were successful only in the presence of an adjuvant (Halbert *et al.*, 1965); (*b*) low molecular weight lens proteins tend to aggregate and precipitate after leakage from the lens (Charlton and van Heyningen, 1968), a phenomenon which favours T-cell activation (Manski, 1973).

Phacogenic uveitis is a sterile inflammation and is supposed to be the result of an immunological reaction to lens remnants present in the aqueous humour, especially after extracapsular lens extraction. This type of uveitis develops sometimes very soon (1 or 2 days) after lens extraction (Schlaegel, 1975), which made us conclude that we are dealing with a secondary immune response, primary sensitisation being evoked by low molecular weight lens crystallins.

We thank Mrs Maria Oerlemans-van Zutphen for her skilful technical assistance.

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Experimental posterior penetrating eye injury in the rabbit. I. Method of production and natural history

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SUMMARY A technique has been developed which produces an experimental posterior penetrating eye injury that reproducibly results in traction retinal detachment in rabbit eyes. The standard injury is an incision through the pars plana with vitreous prolapse and incarceration; the wound is then carefully closed with microsurgical techniques. It appears that blood in the vitreous is an essential factor in the development of vitreous traction and of traction retinal detachment. The model, which has been successfully transferred to Rhesus monkey eyes, is considered useful for further histological, electromicroscopical, electrophysiological, and ultrasound studies of posterior penetrating injuries of the eye. Our immediate goal is to assess in a controlled experiment whether pars plana vitrectomy can interrupt the sequence of events leading to traction retinal detachment after a posterior penetrating injury.

Although the prognosis for penetrating eye injuries has greatly improved, this is largely reflected in injuries which involve only the anterior segment (Moncrieff and Scherible, 1945; Snell, 1945; Roper-Hall, 1959; Remky *et al.*, 1967; Watz and Reim, 1973; Eagling, 1975). Unfortunately there has been little change in the prognosis for injuries to the posterior segment in the past 15 years (Johnson, 1971; Eagling, 1975), and severe injuries involving both the anterior and the posterior segments still result in a blind or excised eye in most cases (Johnson, 1971; Cinotti and Maltzman, 1975; Eagling, 1975). Many of these eyes suffer an expulsive choroidal haemorrhage, with disruption of the intraocular contents and prolapse of the retina, so that there is no potential for visual recovery (Eagling, 1975). However, not all eyes losing useful vision are damaged beyond potential repair; for injuries confined to the posterior segment traction retinal detachment is the main reason for loss of vision (Johnson, 1971; Eagling, 1975; Faulborn *et al.*, 1977).

The development of vitreous traction and traction retinal detachment after a penetrating eye injury has been linked clinically with the presence of vitreous haemorrhage and vitreous incarceration in the wound (Roper-Hall, 1959; Percival, 1972; Johnson, 1971; Eagling, 1975; Faulborn *et al.*, 1977). Clinical and histopathological observations suggest that fibrovascular ingrowth from the scleral wound, vitreous haemorrhage, injury to the lens, and injury to the ciliary body may all contribute to a fibroblastic response within the vitreous, which often progresses to the formation of a cyclitic membrane, in which detached retina may be incorporated (Hogan and Zimmerman, 1964; Coles and Haik, 1972; Eagling, 1975).

It has been postulated that the importance of the vitreous is that it provides a framework or scaffold for fibrosis from other sources. Removal of this scaffold is a rationale for vitrectomy in the treatment of complicated penetrating injuries which involve the posterior segment (Coles and Haik, 1972). Furthermore, after a posterior penetrating injury the blood is typically loculated within the vitreous (Winthrop *et al.*, 1978), and removal of this blood by vitrectomy may reduce the stimulus to inflammation and organisation.

The introduction of pars plana vitrectomy has offered a new approach to the treatment of complicated posterior penetrating injuries (Machemer and Norton, 1972; Michels and Ryan, 1975; Peyman *et al.*, 1975; Benson and Machemer, 1976; Hutton *et al.*, 1976; Faulborn *et al.*, 1977; Conway and Michels, 1978). Yet despite the encouraging preliminary results the indications and optimum timing for vitrectomy remain a matter of controversy. Attempts to address the issues by establishing a

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Table 1 *Natural history of posterior perforating injury in the rabbit eye*

Type of injury	*Number of eyes*	*Length of follow-up*	*Histological appearance*
Standard incision and blood injection	9	3 to 9 days	Retina attached in 9 eyes
	11	12 to 15 days	Retina attached in 3 eyes Retina detached in 8 eyes
	34	18 days to 3 months	Retina attached in 6 eyes Retina detached in 28 eyes
Standard incision and injection of balanced salt solution	15	3 months	Retina attached in 14 eyes Retina detached in 1 eye
Standard incision with injury to the retina	14	2 months	Retina detached with fixed retinal folds* Posterior retinal tears (7 eyes)

randomised controlled clinical trial have been unsuccessful so far (Hutton *et al.*, 1976; Faulborn *et al.*, 1977; Ryan and Allen, personal communication). And certainly the incongruity of penetrating eye injuries with many variables in each individual injury will demand a very large number of patients within a trial to provide a statistically significant result.

Since variables are subject to more precise control in a laboratory environment than in a random patient population, we undertook a study to develop in an experimental animal a model of a posterior penetrating eye injury. Our objective was an injury with the least number of variables, which reproducibly resulted in traction (specifically, nonrhegmatogenous) retinal detachment. The present report describes the method of production and natural history of an experimental posterior penetrating injury in the rabbit eye.

Materials and methods

Pigmented rabbits of either sex, weighing 4 to 5 lb (1·8 to 2·3 kg), were anesthetised by intravenous injection of pentobarbitone; analgesia was obtained by a retrobulbar injection of 0·5 ml saline solution containing 5 mg of lignocaine. The pupils were dilated with 1 drop of cyclopentolate 1% and 1 drop of phenylephrine 10%. The eye was gently prolapsed and secured by a lid suture. Surgery was carried out under sterile conditions and with the magnification of a Zeiss OPMI 6 operating microscope.

The standard wound was a stab incision with a Graefe knife through the pars plana to the centre of the vitreous cavity. This incision was lengthened to 8 mm with scissors, with avoidance of the lens and the peripheral retina. Gel vitreous prolapsed spontaneously through the wound, with rupture of the vitreous face, in a manner similar to that encountered in the perforated human eye. The prolapsed vitreous was abscissed and the wound carefully closed with interrupted sutures of 8–0 silk, with particular attention to good wound apposition. After wound closure the fundus was inspected by indirect ophthalmoscopy and the area of the wound and peripheral retina examined by scleral indentation. Eyes were excluded when the peripheral retina in the area of the wound could not be clearly seen. In some eyes 0·4 ml of autologous blood, drawn immediately beforehand, was injected through a 25-gauge needle inserted through the wound into the midvitreous under ophthalmoscopic control. In others, 0·4 ml of balanced salt solution was injected. The blood or balanced salt solution was injected slowly under low pressure; 0·4 ml could be easily injected without reflux through the wound.

The animals were observed at weekly intervals after surgery. Fundus photographs, descriptions, and drawings of the fundi were made. For histological study eyes were enucleated at varying intervals (Table 1).

Results

During the first week the anterior chamber and vitreous were hazy, but during the second week the media slowly cleared in the eyes without the blood in the vitreous.

STANDARD INCISION AND BLOOD INJECTION

Fifty-four eyes had a standard incision through the pars plana and injection of 0·4 ml of autologous blood into the midvitreous under ophthalmoscopic control. Some eyes were enucleated for histology at 3-day intervals after injury, and others were examined clinically at weekly intervals for up to 3 months (Table 1). At up to 9 days after injury the retina was attached in all 9 eyes examined histologically; at 12 days the retina was detached in 2 out of 4 eyes, and at 15 days the retina was detached in 6 out of 7 eyes that were enucleated (Table 1).

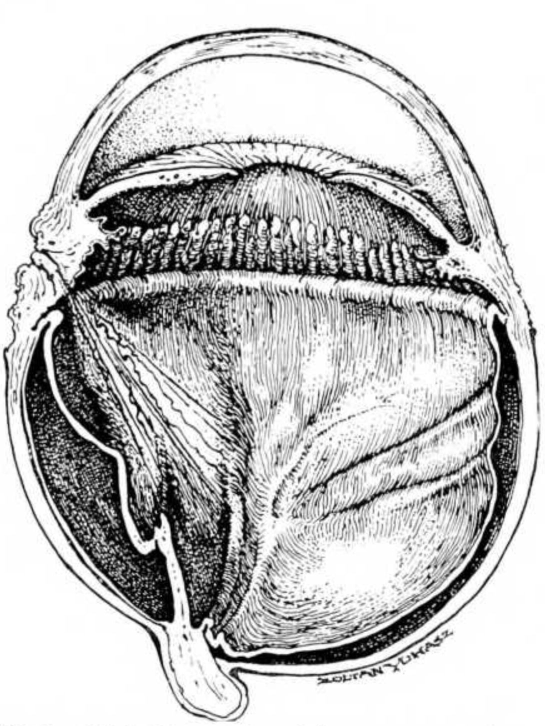

Fig. 1 *Artist's interpretation of the appearance in the rabbit eye at 12 days after injury. There is a subtotal retinal detachment. A condensation of vitreous strands extends from the wound to the posterior retina suggesting anteroposterior vitreous traction. (In the rabbit eye the vitreous is adherent posteriorly in the area of myelinated nerve fibres.) Owing to vitreous traction the peripheral retina has been dragged anteriorly on to the pars plana*

The remaining 34 eyes were enucleated at varying intervals between 18 days and 3 months after injury, and the retina was detached in all but 6 (Table 1).

The fundus appearance was obscured by blood in the vitreous for at least 6 weeks after injury. As the blood cleared, vitreous strands and membranes were observed extending across the anterior vitreous and antero-posteriorly to the retina (Fig. 1). From the wound, scar tissue extended into the vitreous—often on the surface of the adjacent detached retina (Figs. 3 and 4). The clinical findings were confirmed by gross examination of the enucleated eyes with the dissecting microscope. It was possible to identify changes in the vitreous with strands of vitreous extending from the wound to the posterior retina (Fig. 1), and strands extending from the wound to the peripheral retina in the area of the vitreous base (Fig. 2). The configuration of the retinal detachment suggested the presence of vitreoretinal traction; the earliest appearance was of traction from the wound to the posterior retina, resulting in elevation of the area of the medullary rays (Fig. 1), and the late appearance was of total retinal detachment with the entire retina drawn up into the area of the wound (Fig. 4). The peripheral retina showed a characteristic appearance of being dragged forward towards the wound. This characteristic rolling forward of the peripheral retina on to the pars plana might involve its entire circumference (Fig. 2).

STANDARD INCISION AND INJECTION OF BALANCED SALT SOLUTION

Fifteen eyes had a standard incision through the pars plana and injection of 0·4 ml of balanced salt solution. These eyes were documented clinically for 3 months after injury (Table 1). Vitreous strands or membranes were not identified by ophthalmoscopy in these eyes, nor was fibrous proliferation from the area of the wound into the vitreous. One eye had a spontaneous vitreous haemorrhage at the time of the incision, and 4 weeks later, when the vitreous haemorrhage had cleared, a traction retinal detachment was observed. In the other 14 eyes the retinas remained attached.

STANDARD INCISION WITH INJURY TO THE RETINA

Fourteen eyes suffered unintentional retinal damage at the time of injury, either by disinsertion of the peripheral retina adjacent to the wound or by direct laceration of the retina. During the incision through the pars plana 10 of these eyes suffered a spontaneous choroidal and subretinal haemorrhage, and the blood ruptured through the peripheral retina so that torn retina was prolapsed into the wound. In the other 4 eyes the standard incision was too far posterior and involved the peripheral retina. Retinal

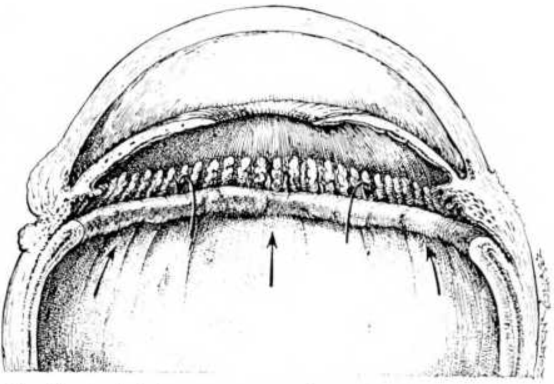

Fig. 2 *Artist's interpretation of the characteristic rolling forward of the peripheral retina on to the pars plana owing to traction on the vitreous base*

detachment was total in 10 eyes and incomplete in 4. Typically, at 3 to 4 weeks after injury these eyes showed the appearance of fixed retinal folds, starfolds, pigment granules on the surface of the retina, and funnel-type retinal detachments. In 4 eyes large posterior retinal tears occurred and in 3 eyes smaller oval tears. These retinal tears were not identified at the time of injury.

Discussion

For penetrating injuries which are confined to the posterior segment traction retinal detachment is the main reason for loss of vision (Eagling, 1975; Hutton *et al.*, 1976; Benson and Machemer, 1976; Faulborn *et al.*, 1977). The experimental injury in the rabbit eye incorporates few variables and results in traction retinal detachment which is highly reproducible. Progressive detachment of the retina has been produced previously in experimental animals but usually as a result of retinal hole formation (Foulds, 1963; Machemer and Norton, 1968). By contrast, our specific aim was to produce traction retinal detachment and to avoid direct damage to the retina, thus excluding rhegmatogenous retinal detachment as another variable.

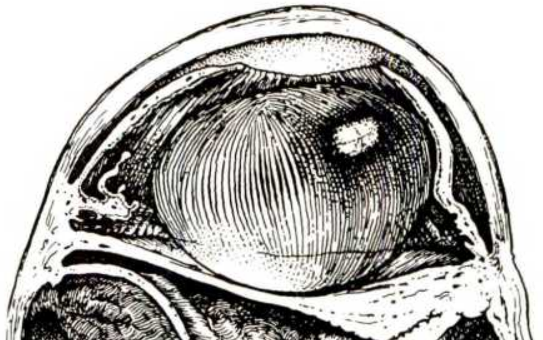

Fig. 3 *Artist's interpretation of the appearance in the rabbit eye at 4 weeks after injury. The retina is totally detached, and a prominent fibrous ingrowth from the wound has formed a cyclitic membrane*

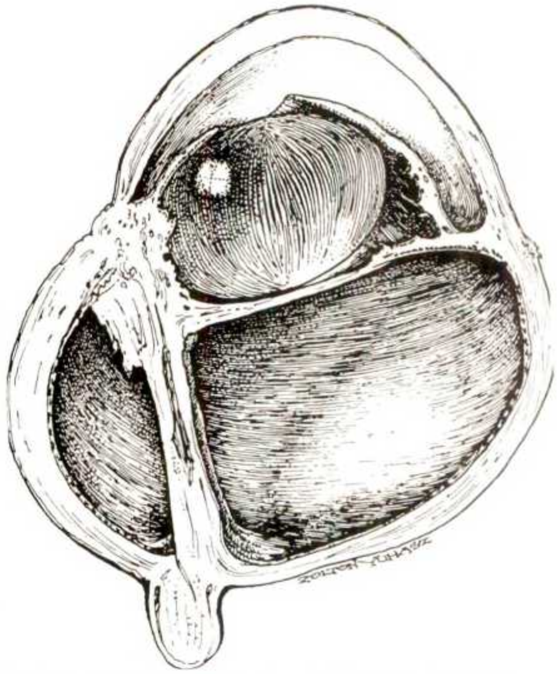

Fig. 4 *Artist's interpretation of the appearance at 6 weeks after injury. There is a total retinal detachment, with the retina drawn up into the wound and incorporated into the fibrous ingrowth*

Injection of blood into the rabbit vitreous by a needle puncture alone may result in retinal detachment due to a posterior retinal tear (Freilich *et al.*, 1966) or related to the growth of scar tissue into the vitreous along the needle track and subsequent traction on the retina (Constable, 1975; Swan, 1977). In preliminary experiments we investigated the effects of a single injection of autologous blood into the rabbit vitreous by a needle puncture, but we were unable to produce traction retinal detachment with the reproducibility that we desired (Cleary and Ryan, 1978). Furthermore, since some vitreous loss is a frequent accompaniment of penetrating trauma, it was felt desirable to include this as a component of the experimental model.

In the rabbit eye, after injury and intravitreal blood injection, retinal detachment occurred typically at between 12 and 15 days. During the development of retinal detachment the configuration of the peripheral and posterior retina, as well as the orientation of vitreous strands, suggested the presence of vitreous traction. The characteristic rolling forward of the peripheral retina, which might involve its entire circumference (Fig. 1), might be related to vitreoretinal adhesion in the area of the vitreous base. Similarly, the early detachment of the posterior retina could be attributed to anterior-posterior vitreous traction related to the vitreoretinal adhesion in the area of the medullary rays in the posterior fundus of the rabbit.

We have observed a similar appearance of traction on the peripheral retina in the region of the vitreous base not only in rabbit eyes but also in monkey eyes and in human eyes enucleated after penetrating injuries (Cleary and Ryan, 1978; Winthrop *et al.*, 1978). Clinically we have also observed in patients after a posterior penetrating injury that this characteristic dragging forward of the peripheral retina on to the pars plana may precipitate and be the only cause of total retinal detachment. In the human eye, however, unlike the rabbit's, the cortical vitreous is not so adherent to the posterior retina (Foos, 1975), and typically, after a posterior penetrating injury, the vitreous becomes detached posteriorly without subsequent direct traction on the posterior retina. The exception is a double perforating injury with incarceration of vitreous in both the anterior and posterior wound, when antero-posterior vitreous traction may be observed.

In this study, although our aim was to avoid direct damage to the retina, in some eyes the peripheral retina was involved in the standard incision, while in others a profuse choroidal and subretinal haemorrhage occurred at the time of injury, and blood ruptured through the peripheral retina, disinserting it. This expulsive type of haemorrhage in the rabbit eye has its counterpart in the most severe penetrating injuries in human eyes (Eagling, 1975; Barry, 1975).

In eyes with clear media, and retinal tears and funnel-shaped retinal detachments, we observed the appearance of fixed retinal folds and starfolds with pigment on the surface of the retina. The clinical appearance resembled massive periretinal proliferation (Machemer and Lagua, 1975). The histopathological features will be reported in detail in a separate communication.

The experimental evidence in this study supports clinical observations on the importance of blood in the vitreous in the development of vitreous traction and, ultimately, traction retinal detachment after a posterior penetrating eye injury (Johnson, 1971; Percival, 1972; Eagling, 1975; Faulborn *et al.*, 1977). We have successfully transferred this method of experimental posterior penetrating injury to rhesus monkey eyes and have shown that traction retinal detachment is also highly reproducible in the primate eye. We believe that this experimental model can provide much information of clinical relevance and the opportunity to examine mechanisms which underlie the development of traction retinal detachment. The many variables which complicate penetrating injuries may be isolated and investigated, such as the effects of vitreous loss, the role of blood and its different components in the vitreous, the effects of lens injury, and the admixture of lens material and vitreous. It will be of value to have precise histopathological correlation of ultrasound and bright-flash electroretinographic findings. Finally, we shall investigate in a controlled experiment the role and optimum timing for vitrectomy in the treatment of a posterior penetrating injury.

We thank Ms Kate Borkowski for technical assistance and Mr Zoltan Yuhasz for the illustrations.

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Experimental posterior penetrating eye injury in the rabbit. II. Histology of wound, vitreous, and retina

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SUMMARY The histological findings of the wound, the vitreous, and the retina in the rabbit eye with experimental posterior penetrating injury are described. Wound healing had just begun at 3 days after injury and was well established by 9 to 12 days. It involved proliferation of cells from the episclera and from the choroid. The progression to a fibrous ingrowth from the wound occurred only in eyes with blood in the vitreous. The intravitreal fibroblastic proliferation had begun at 6 days after injury and seemed to be derived from the choroid, the nonpigmented ciliary epithelium and, posteriorly, from the optic nervehead. During the development of retinal detachment the configuration of the peripheral and posterior retina, together with the orientation of vitreous strands, suggested the presence of vitreous traction. We postulate that the presence of contractile fibroblasts (myofibroblasts) in the vitreous may provide the mechanism for vitreous traction. The retinal detachments were also characterised by epiretinal and subretinal membranes, but these were not prominent. The end-stage appearance of a soft, shrunken eye with cyclitic membrane formation and retinal detachment resembles the outcome in many human eyes after severe penetrating injuries.

Severe penetrating injuries in human eyes are characterised histologically by intraocular fibrosis with cyclitic membrane formation and traction retinal detachment (Hogan and Zimmerman, 1962; Coles and Haik, 1972). In fact, traction retinal detachment is the main reason for loss of vision in those injuries which are confined to the posterior segment (Eagling, 1975).

It has been shown in the preceding paper (Cleary and Ryan, 1979) that the experimental model of a posterior penetrating injury in the rabbit eye results in cyclitic membrane formation and in traction retinal detachment. In the present paper we describe the sequence of histological changes.

Materials and methods

As previously described, rabbit eyes were injured by a standard wound which was 8 mm long through the pars plana, avoiding the lens and the peripheral retina. Prolapsed vitreous was abscissed and the wound carefully closed by microsurgical techniques with interrupted sutures of 8–0 silk. After wound closure the fundus was inspected by indirect ophthalmoscopy and the area of the wound and the peripheral retina examined by scleral indentation. In some eyes autologus blood and in others balanced salt solution was injected through a 25-gauge needle inserted through the wound and under ophthalmoscopic control into the mid-vitreous, with avoidance of the lens and the retina.

The eyes were enucleated at 3-day intervals for the first 3 weeks after injury as well as at 2 and 3 months after injury. Each group consisted of a minimum of 3 eyes. The eyes were fixed in Bouin's fixative for 24 hours and were then sectioned through the optic nerve and midpoint of the wound for gross examination. Each half eye was examined under the dissecting microscope, and drawings and photographs were made. The eyes were then slowly dehydrated in alcohol and embedded in paraffin.

Vertical serial sections of 5 μm thickness were made through the wound, through the retina, and through the optic disc. The sections were stained with haematoxylin-eosin, periodic acid Schiff, and trichrome after Masson.

Controls included 7 normal eyes and 15 eyes with a standard injury but without blood injection.

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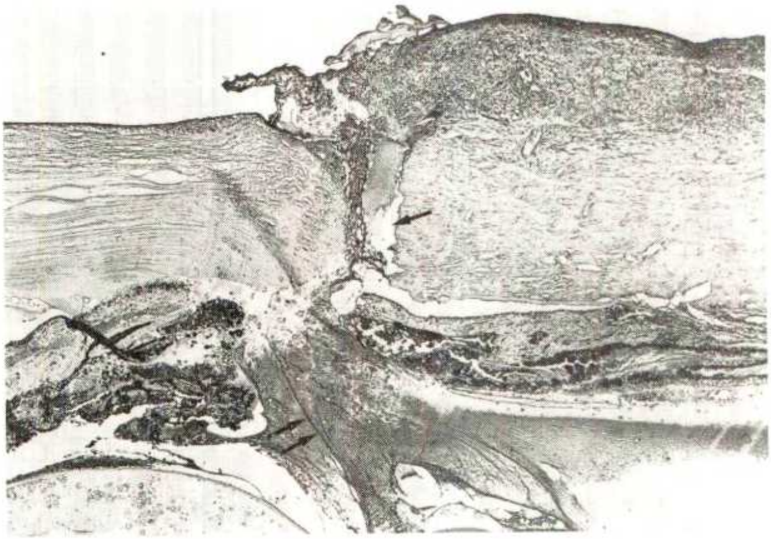


Fig. 1 *At 3 days after injury. The wound has been artifactually separated during processing (arrow). The striking features are the evidence of proliferation from the episcleral tissues into the wound, and the incarceration of vitreous with vitreous strands radiating from the wound (double arrow) (H and E, × 28)*

Results

STANDARD INCISION AND BLOOD INJECTION

Early phase (0 to 3 days)

At 3 days after injury the wound and vitreous in the inner aspect of the wound were infiltrated with leucocytes and macrophages (Fig. 1). The edges of the scleral wound remained clearly defined, and there was some early evidence of wound healing with proliferation from the episclera (Fig. 1). Vitreous was incarcerated in the wound, and strands of vitreous radiated from the wound to the posterior retina and also to the peripheral retina in the area of the vitreous base (both directly posterior to the wound and at 180 degrees from the wound). At this stage intravitreal fibroblastic proliferation was not seen.

In these eyes the retina was attached, and the configuration of the peripheral retina resembled that of the normal control eyes and did not suggest the presence of vitreous traction.

Intermediate phase (6 to 15 days)

From 6 to 15 days after injury cellular proliferation occurred and became progressively more prominent at the wound and within the vitreous. In most of these eyes the retina was detached.

During this phase the blood clot became more diffuse and showed signs of absorption, but it remained loculated within the vitreous. The vitreous did not separate posteriorly from the retina. Haemosiderin-containing macrophages were present within the vitreous and in the inner retina.

Wound healing involved proliferation of cells from the episclera initially, but in the inner aspect of the wound fibroblastic proliferation occurred from the uvea and also from proliferation of the nonpigmented ciliary epithelium. Even with good wound apposition fibroblastic ingrowth was already present at 6 days after injury and was prominent by 12 days (Figs. 2 and 3). The fibroblasts permeated the blood clot and lined up along the vitreous strands, which were incarcerated in the wound (Figs. 2 and 3). Fibroblastic proliferation into the vitreous also occurred posteriorly from the optic nervehead, where the fibroblasts were also lined up along the vitreous strands (Figs 2 and 3).

During the development of retinal detachment the configuration of the peripheral and posterior retina, together with the orientation of vitreous strands, suggested the presence of vitreous traction (Figs. 4, 5, 6). At 6 days after injury, but more prominently at 9 and 12 days, the peripheral retina assumed a characteristic appearance of being dragged or rolled forward on to the pars plana, not only directly posterior to the wound but also at 180 degrees from the wound (Figs. 5 and 6). In fact, this rolling forward of the peripheral retina was present throughout its entire circumference. Vitreous strands were attached to these areas of peripheral retina, and the vitreous was lined up between the retina and the wound (Figs. 5 and 6). Detachment of the posterior retina occurred typically at 12 days after injury, with a similar appearance of lining up of vitreous strands between the wound and the detached posterior retina.

Late phase (18 days to 3 months)

Eyes examined between 18 days and 3 months after injury showed progression from the initial stages of

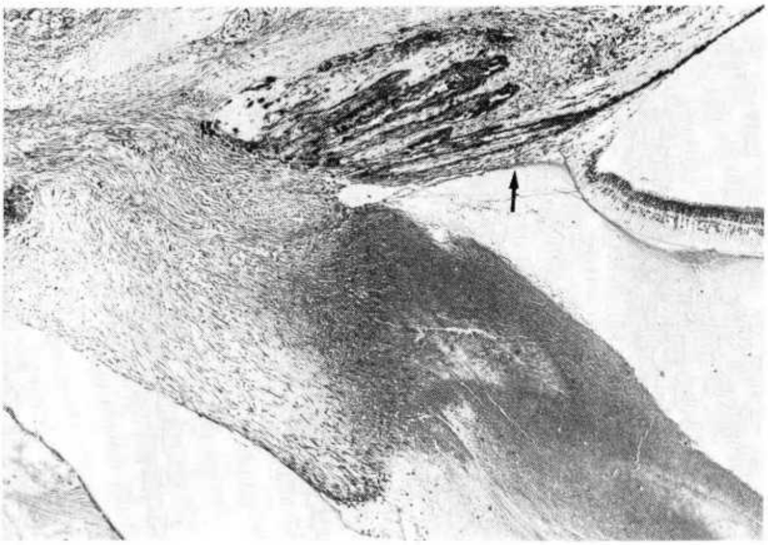


Fig. 2 *At 12 days after injury. Note the marked fibrous proliferation extending inward from the wound. The ciliary processes are drawn up to the wound. There is a proliferation of the nonpigmented ciliary epithelium (arrow). The fibroblastic proliferation has invaded the blood clot and is extending posteriorly along the vitreous condensation. In the rabbit eye after injury the vitreous does not separate from the posterior retina, and vitreous becomes condensed and lined up between the wound and the posterior retina. (H and E, × 30)*

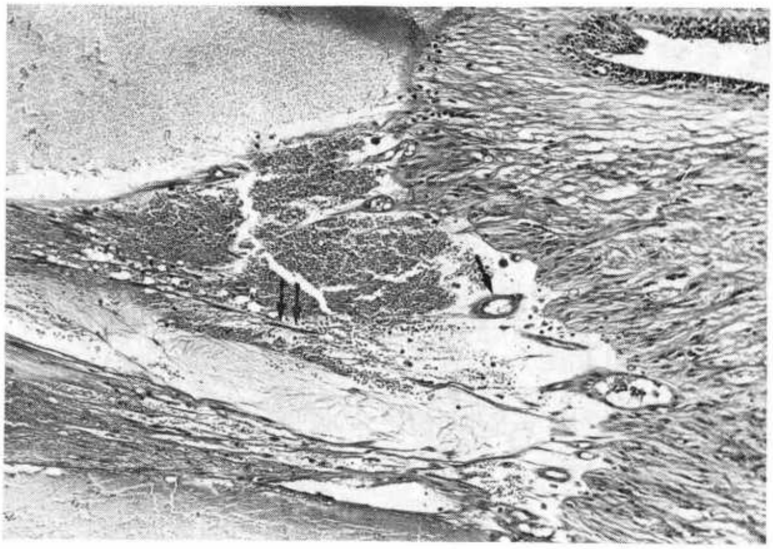


Fig. 3 *The same eye as Fig. 2 at 12 days after injury. This photograph shows the attachments of the vitreous over the optic nerve head. The blood vessels which are normally present on the surface of the nerve are apparent (arrow). Vitreous strands are attached to the surface of the optic nerve head, and the remarkable feature is the organisation of fibroblasts with their long spindle-shaped nuclei along the vitreous strands (double arrow). (H and E, × 60)*

retinal detachment to the advanced stage of total retinal detachment, with the retina drawn up into the wound, with cyclitic membrane formation (Figs. 7 and 8), ciliary body and choroidal detachments, and finally the development of an atrophic shrunken eye.

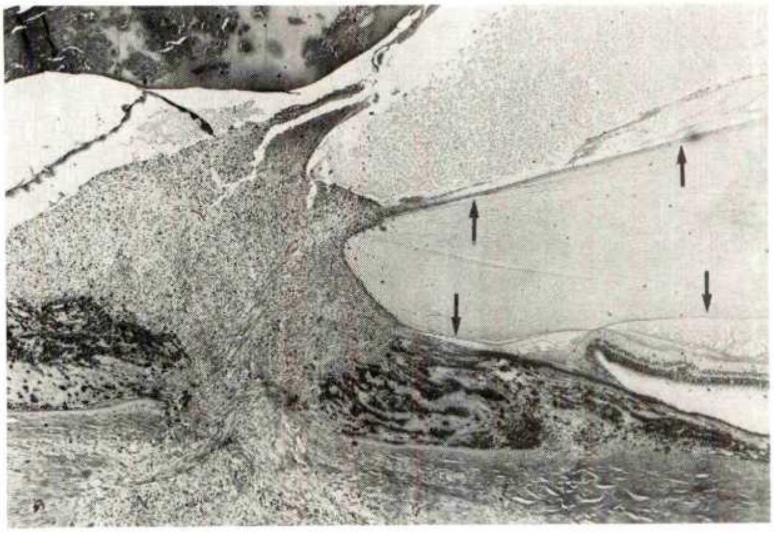
Proliferations on the surface of the retina with the formation of epiretinal membranes were identified occasionally at 18 and 21 days after injury. However, when the retinal detachments became total and the retina was convoluted and drawn up into the wound, it was not possible to identify discrete epiretinal or subretinal membranes.

Hyperplasia of the retinal pigment epithelium was frequent, with sheets of flattened pigmented cells and plaques of spindle-shaped cells (Fig. 9). In addition, these eyes were characterised histologically by a focal nongranulomatous inflammatory infiltration of the choroid.

STANDARD INCISION AND INJECTION OF BALANCED SALT SOLUTION

These eyes demonstrated uncomplicated healing of the wound, which had started at 3 days after injury and was well established by 21 days. Proliferation from the episclera appeared as the initial response

Fig. 4 *At 12 days after injury. The fibrous proliferation from the wound is quite prominent. The fibrous ingrowth appears to be derived from the uvea and also from the scleral wound. Note the lining up of the condensed vitreous fibrils which extend from the wound to the posterior retina (arrows). There are a number of inflammatory cells in the vitreous, and overlying the vitreous is the blood clot which is in the process of lysis and organisation. (H and E, ×23)*



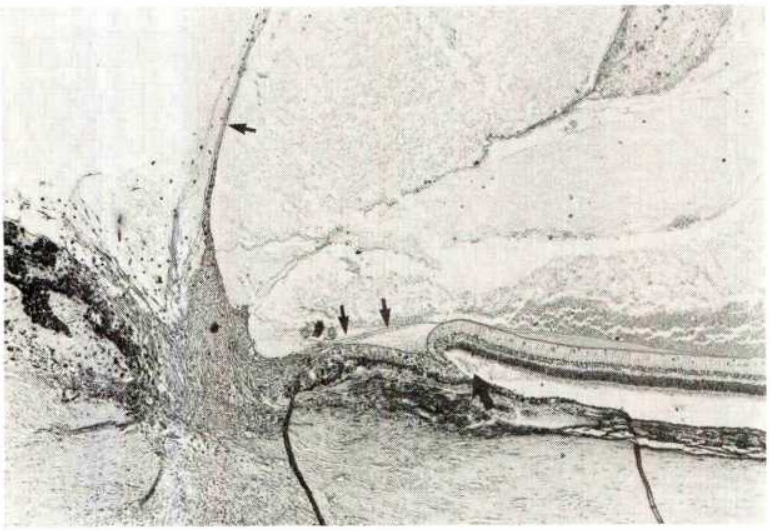
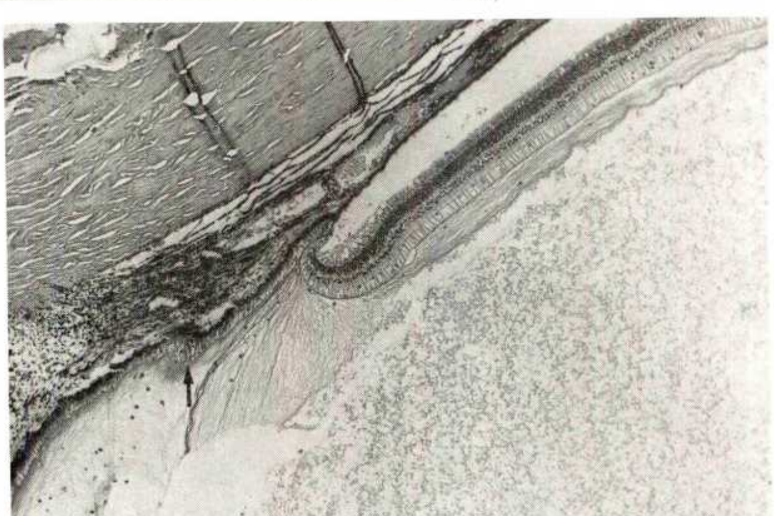


Fig. 5 *At 12 days after injury. The lens has been lost during processing. The wound in this animal illustrates a less luxuriant fibrous proliferation. None the less the incarceration of vitreous in the wound and the proliferation of fibroblasts along the anterior vitreous are quite apparent (arrow). The vitreous is condensed in the region of the vitrous base, and strands of vitreous extend between the wound and the peripheral retina (double arrow). The peripheral retina has rolled forward on to the nonpigmented ciliary epithelium. There is a real retinal detachment in the periphery as evidenced by serous fluid beneath the sensory retina (broad arrow). (H and E, ×28)*

Fig. 6 *The same eye as Fig. 5 at 12 days after injury. At 180 degrees from the wound the peripheral retina has also rolled forward on to the nonpigmented ciliary epithelium. The condensation of vitreous over the peripheral retina and vitreous base is quite striking. Note again the lining-up of vitreous fibrils and the organisation of inflammatory cells within this matrix. The nonpigmented ciliary epithelium shows a suggestion of early proliferation (arrow). (H and E, ×37)*



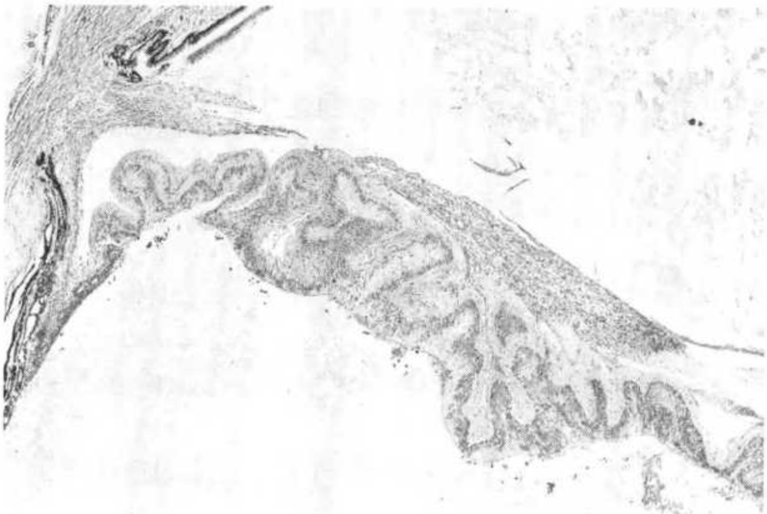


Fig. 7 *At 21 days after injury. The lens has been lost during processing. Fibrous proliferation from the wound appears to be derived mainly from the uveal tract. The retina has been thrown into folds and is drawn up to the wound by this fibrous proliferation. The fibrous tissue in the process of forming a cyclitic membrane extends along the surface of the detached retina. (H and E, × 20)*

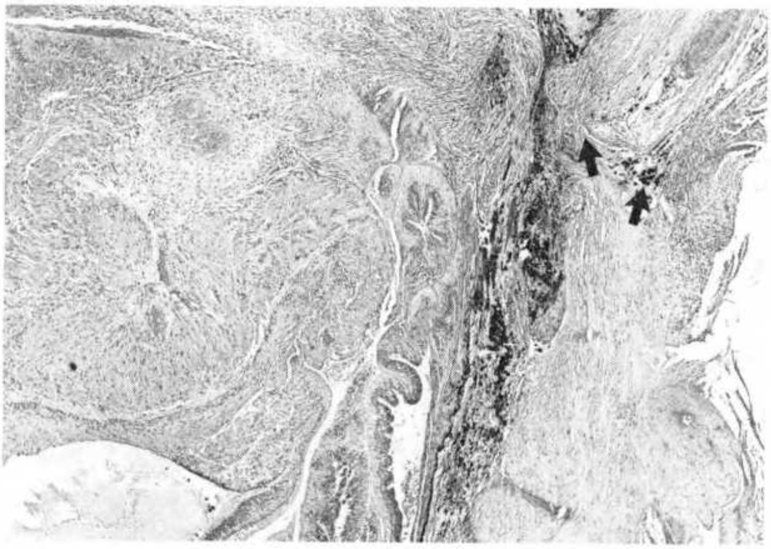


Fig. 8 *Another eye showing the end stage appearance at 4 weeks after injury. The wound is organised and has blood vessels and scattered pigment in the new fibrous tissue (arrows). A marked fibrous proliferation extends inwards from the wound, and swirls of fibrous tissue form a plaque on the surface of the retina. In this animal the entire retina is drawn up into the region of the wound and fibrous proliferation. (H and E, × 56)*

in wound healing, but fibroblastic proliferation from the choroid, together with proliferation of the nonpigmented ciliary epithelium, was also present. Some cellular proliferation occurred on the inner vitreal aspect of the wound, but it did not show progression, and fibroblastic proliferation within the vitreous was not seen (Fig. 10).

Vitreous strands were incarcerated in the wound, and they were also attached to the posterior retina and to the peripheral retina in the region of the vitreous base. The configuration of the retina, however, did not suggest evidence of vitreous traction (Fig. 10).

Eyes examined at 3 months after injury showed a healed and remodeled scar, an attached retina, and the absence of fibrous ingrowth. Some eyes showed proliferation of the nonpigmented ciliary epithelium just posterior to the wound.

STANDARD INCISION WITH INJURY TO THE RETINA

Typically, wound healing was uncomplicated, and, although vitreous was incarcerated in the wound, neither a fibrous ingrowth from the wound nor intravitreal fibrous proliferations were seen.

The detached retina showed the usual associated

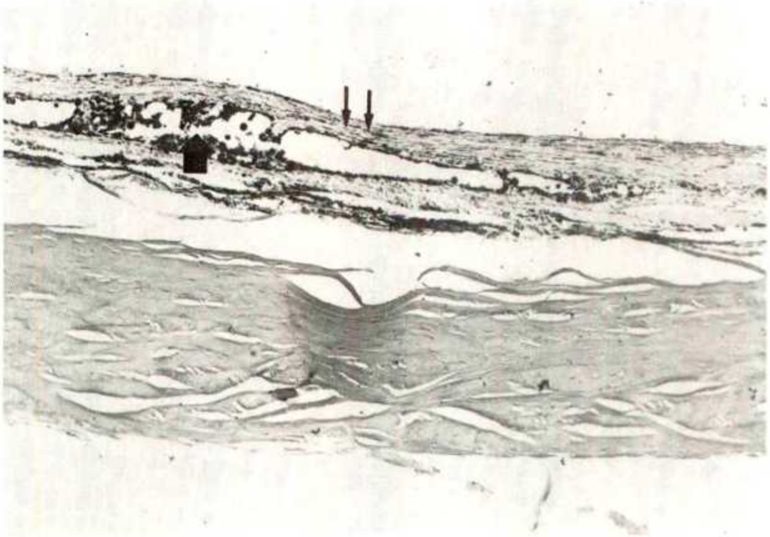


Fig. 9 *At 2 months after injury. Hyperplasia of the retinal pigment epithelium has occurred. Note the tubular proliferation of the retinal pigment epithelium cells (arrow). Note the overlying plaque of partially depigmented spindle cells (double arrows), presumably laid down by the pigment epithelium during its proliferation into the subretinal space. (H and E, ×22)*

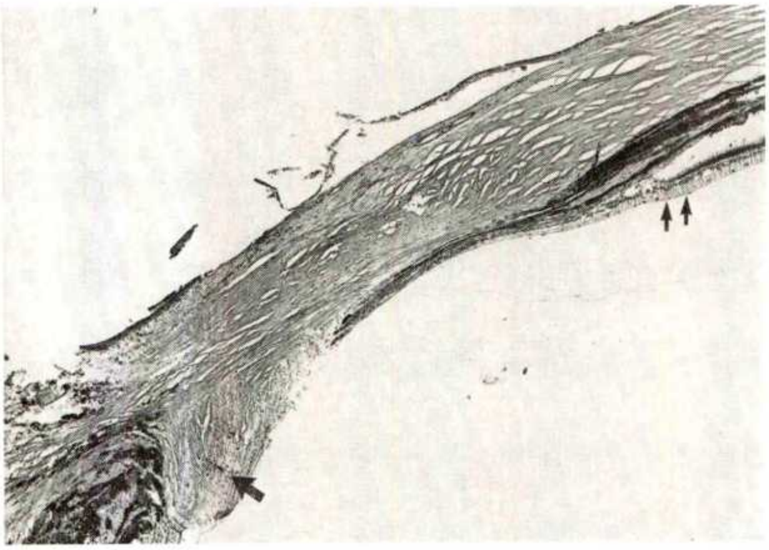


Fig. 10 *At 3 months after injury and injection of balanced salt solution. The wound has healed and is remodelled. There is a limited fibrous proliferation at the site of penetration of the pars plana and ciliary body (arrow). There has been a sliding forward of the nonpigmented ciliary epithelium in the region of the wound. More importantly, the retina is noted to be in a normal position without detachment (double arrows). This view of the peripheral retina is also noteworthy in that the same means of fixation as well as histopathological techniques were employed as for all other eyes. Thus we can feel confident that the rolling forward of the peripheral retina on to the pars plana ciliary epithelium observed in eyes with a standard injury and blood injection is not an artifact due to processing. (H and E, ×26)*

degenerative changes, with loss of photoreceptors and intraretinal cystoid swelling. In some areas the retina was thrown into folds, which could be related to the presence of epiretinal membranes. However, the configuration of the retinal detachment remained funnel shaped, and the retina was not drawn up into the wound.

As early as 21 days after injury epiretinal membranes were found, which in some eyes were connected to the underlying retina by a small bridge of tissue and which contained cells with abundant cytoplasm and oval-to-spindle-shaped nuclei. In other eyes the epiretinal membranes may have originated from the prepapillary blood vessels (Fig. 11). The epiretinal membranes also contained pigmented cells which stained positive with Prussian blue for iron. These cells had the appearance of haemosiderin-laden macrophages.

Subretinal membranes lying outside the external limiting membrane could also be found as early as

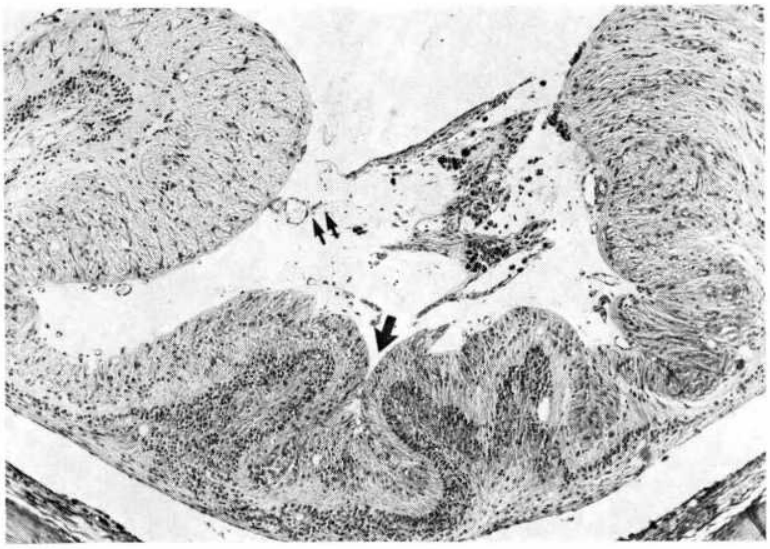


Fig. 11 *At 2 months after injury. Full-thickness retinal folds are present. The medullated and nerve fibre layers have been pulled close to each other and approximated in one region (arrow). The epiretinal membrane consists of cells with abundant cytoplasm and oval nuclei which may be glial in origin, and also contains pigmented haemosiderin-laden macrophages. In addition the epiretinal membrane has continuity with the blood vessels which are normally present on the surface of the medullary rays in the rabbit eye (double arrows). (H and E, × 45)*

21 days after injury, but were very uncommon and were confined to retinal folds (Fig. 12). Within retinal folds it was more common to observe a proliferation in the outer retina, of irregularly arranged cells with abundant cytoplasm and oval or spindle-shaped nuclei, but lying within the external limiting membrane (Fig. 12). These cells had displaced the outer retinal layers from the external limiting membrane to the inner nuclear layer.

When the retina was detached, proliferation of the retinal pigment epithelial cells was common and was observed as early as 15 days after injury. Both diffuse hyperplasia with sheets of flattened pigmented cells and plaques of partially depigmented, closely packed, spindle-shaped cells were seen (Fig. 9). When the retinal detachment extended anteriorly to the ora, the pigment epithelium proliferated in the area of the detached pars plana epithelium, becoming 2 or 3 layers thick with irregularly arranged depigmented cells.

Two additional eyes that suffered spontaneous choroidal and subretinal haemorrhage during the injury were enucleated immediately after wound closure. These eyes had a choroidal vascular bed that was engorged with blood.

Discussion

In experimental posterior penetrating injury in the rabbit eye we observed intraocular fibrous proliferation, the formation of cyclitic membranes, and the development of traction retinal detachment. Human eyes suffer the same sequelae after severe posterior penetrating injuries, although the time course is quite different (Coles and Haik, 1972; Eagling, 1975; Winthrop *et al.*, 1978). The evolution of the pathological process can be conveniently divided into 2 stages.

(1) FIBROUS INGROWTH AND INTRAVITREAL FIBROUS PROLIFERATION

The process of wound healing and repair with proliferation from the episclera and choroid had just begun at 3 days after injury and was well advanced by 9 days, which accords with previous observations (Duke-Elder, 1965). However, the presence of blood in the vitreous had a major effect in the development of a fibrous ingrowth from the wound. In eyes without blood in the vitreous healing of the scleral wound was rapid and the resultant scar was inconspicuous. By contrast, in the eyes with blood in the vitreous, the progression to an intraocular fibrous ingrowth from the wound was a constant feature. Other factors are recognised as important in the development of a fibrous ingrowth, such as incarceration of tissues and poor wound apposition (Duke-Elder, 1965). Yet in these experiments despite good wound apposition a prominent fibrous ingrowth was typical.

During intravitreal fibrous proliferation the cells appeared to line up along vitreous strands as a scaffolding. Cellular proliferation into the vitreous from the wound appeared to be derived not only from the episclera and choroid, but also from the non-pigmented ciliary epithelium (Fig. 14). These cells hypertrophy and become elongated and may proliferate along the vitreous strands to which they are attached. The normal nonpigmented ciliary

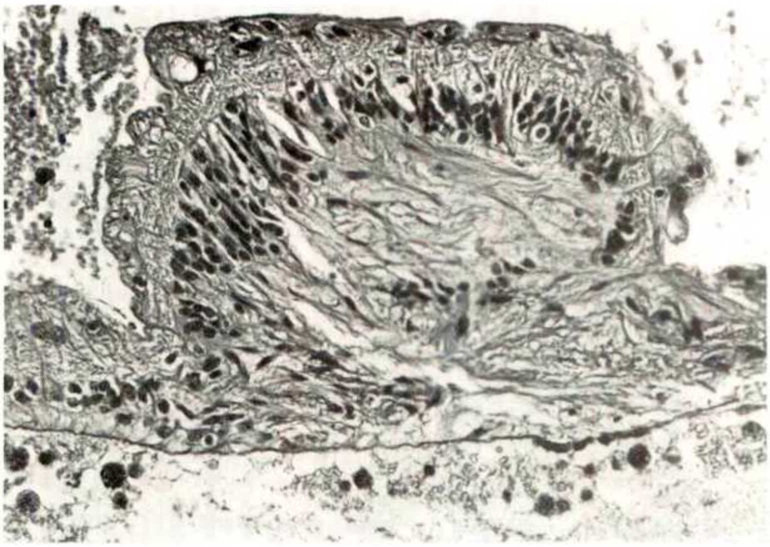


Fig. 12 *At 3 months after injury. Note the external limiting membrane delimits the outer retina. An intraretinal glial proliferation has occurred, containing irregularly arranged cells with abundant cytoplasm and oval-to-spindle-shaped nuclei. Inflammatory cells, macrophages, and polymorphonuclear leucocytes are present in the subretinal space. (H and E, × 123)*

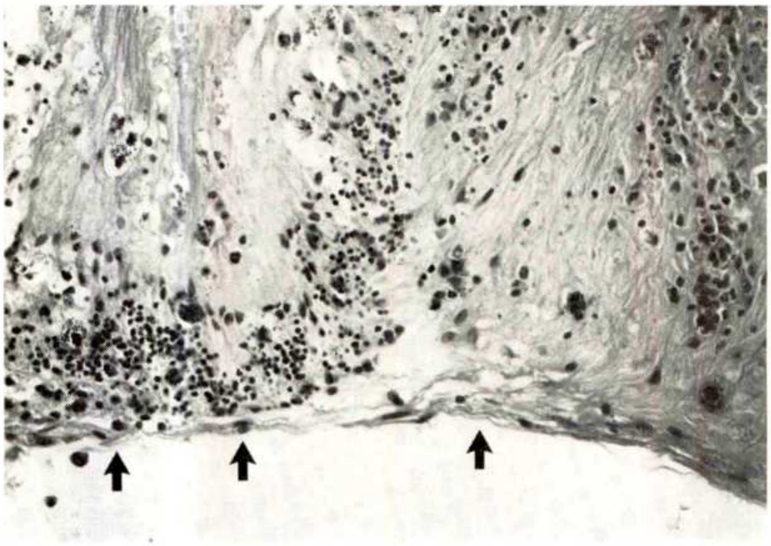


Fig. 13 *At 3 weeks after injury. Note the absence of the external limiting membrane. There is a proliferation of glial cells extending from the outer aspect of one retinal fold to another (arrows). These cells contain abundant cytoplasm and long processes and oval-to-spindle-shaped nuclei. (H and E, × 154)*

epithelium may give rise to collagen fibrils in the vitreous (Fine and Zimmerman, 1963), and hyperplasia of these cells is recognised in a variety of conditions, including injury and inflammation (Hogan and Zimmerman, 1962).

Intravitreal fibrous proliferation from the optic nervehead has been observed previously in rabbit eyes after injection of autogenous blood or saccharated iron oxide (Cibis and Yamashita, 1959). This proliferation may be derived from epipapillary glial tissue or, more likely, from the prepapillary blood vessels.

The eyes which contained blood also contained monocytes and macrophages; and it is possible that fibroblasts may be derived from haematogenous cells, particularly monocytes and macrophages (Allgower and Hullinger, 1960), although most of the experimental evidence now supports the view that fibroblasts involved in wound healing are derived locally (Grillo, 1964). It is also possible that cells which originated in the pigment epithelium in the area of the wound may have contributed to the fibrous ingrowth, and we observed some spindle-shaped cells with pigment other than haemosiderin in their cytoplasm. Certainly, 'fibrous metaplasia' of pigment epithelium is not uncommon (Hogan and

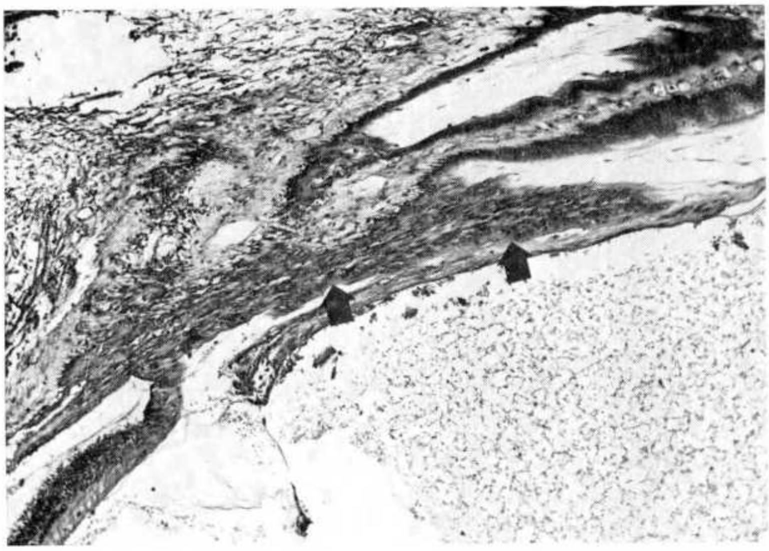


Fig. 14 *At 21 days after injury the appearance of the ciliary body at 180 degrees from the wound in an eye with a subtotal retinal detachment. This photograph shows proliferation of the nonpigmented ciliary epithelium. The appearance cannot be explained on the basis of tangential cutting alone, which is apparent in 1 ciliary process. The number of cells and their nuclei suggest a real proliferation of the nonpigmented ciliary epithelium cells. (H and E, × 50)*

Zimmerman, 1962; Freyer, 1966; Wallow and Tso, 1972; Tso, 1973; Machemer and Laqua, 1975), but recognition of the epithelial characteristics of these 'fibrocyte-like' cells can be demonstrated only by electron microscopy (Wallow and Tso, 1972; Machemer and Laqua, 1975).

(2) TRACTION RETINAL DETACHMENT

In the rabbit eyes, with experimental posterior penetrating injury and blood in the vitreous, we have suggested that the development of retinal detachment may be related to vitreous traction. We interpreted the characteristic configuration of the peripheral retina and elevation of the posterior retina, which was confined initially to the medullary rays, as evidence of vitreoretinal traction (Figs. 4, 5, 6). The lining up of vitreous strands between the wound and posterior retina and between the wound and peripheral retina in the region of the vitreous base suggests a mechanism by which traction is effected. Certainly in the rabbit eye it is apparent during vitrectomy that the vitreous is tightly attached not only over the peripheral retina in the vitreous base but also over the posterior retina in the region of the medullary rays.

The onset of traction retinal detachment at about 12 days after injury coincides with the presence of significant intravitreal fibroblastic proliferation. In fact fibrous proliferation within the vitreous was present at 6 days after injury but showed a significant progression by 9 to 12 days. Although we have implicated vitreous traction in the development of retinal detachment, the mechanism for traction is obscure but is perhaps related to changes in vitreous collagen, such as reorientation of collagen fibrils as a result of changes in cross-linkage between the native vitreous collagen and the new collagen laid down by fibroblasts.

On the other hand it has been shown that wound contraction occurs independently of collagen formation (Abercrombie *et al.*, 1956) and is mediated by fibroblasts with characteristics typical of smooth muscle cells—myofibroblasts (Gabbiani *et al.*, 1972). The presence of such contractile fibroblasts in the vitreous could provide a mechanism for vitreous traction. Furthermore, the development of vitreous traction leading to traction retinal detachment in the rabbit eye at about 12 days after injury coincides with the rapid increase in the percentage of myofibroblasts observed at between 1 and 2 weeks in experimental full-thickness skin wounds (Rudolph *et al.*, 1977). Although we have not performed electron microscopy on the injured rabbit eyes, we have observed typical myofibroblasts in rhesus monkey eyes after an experimental posterior penetrating injury.

Epiretinal and subretinal membrane formation complicates many posterior penetrating injuries in human eyes (Winthrop *et al.*, 1978). In some contraction of epiretinal membranes at the macula results in macular pucker, while in others massive periretinal proliferation leads to inoperable retinal detachment (Hutton *et al.*, 1976; Benson and Machemer, 1976; Faulborn *et al.*, 1977; Winthrop *et al.*, 1978). In the rabbit eye epiretinal membranes were not common and were probably glial in origin, as indicated by the bridges connecting the epiretinal fibrous tissue and the retina. In human eyes the development of epiretinal fibrosis and surface wrinkling retinopathy has been linked with detachment of the posterior vitreous (Roth and Foos, 1971; Wise, 1975; Gass, 1977), though the relationship is far from clear (Foos, 1977). It is of interest, therefore, that in the rabbit eye posterior vitreous detachment does not occur, and we have commented on the tight attachment between the vitreous and posterior retina over the medullary rays.

It is recognised that subretinal membrane in both human and monkey eyes can have their origin in the retinal pigment epithelium (Machemer and Laqua, 1975; Machemer *et al.*, 1978). In the rabbit we noted that proliferation of pigment epithelial cells was common in eyes in which the retina was detached. Nonetheless we found subretinal membranes infrequently in the rabbit eyes, while their appearance and continuity with the retina and a total lack of pigmentation suggested a glial cell rather than pigment epithelium cell origin.

The rabbit eyes enucleated at 3 months after a standard injury and blood injection were soft, the anterior chamber was frequently absent, the lens was often cataractous, the retina was detached, and a cyclitic membrane was present. This end-stage appearance resembles the atrophy and shrinkage seen in many human eyes enucleated after severe ocular trauma (Hogan and Zimmerman, 1962).

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One model of outflow damage

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SUMMARY The intraocular pressure, facilities of outflow, and Po/C ratios of 3 groups of eyes were compared. Group 1 consisted of 20 eyes at risk to the development of acute closed-angle glaucoma that had been treated with prophylactic pilocarpine for at least 8 years. Group 2 consisted of 20 eyes at risk that had received no treatment and had been followed up for at least 4 years. Group 3 comprised 20 eyes in which there was no evidence of glaucoma. There were highly significant differences between the 3 groups. The 60 eyes were then provoked with pilocarpine and phenylephrine; 90% of Group 1, 75% of Group 2, and none of Group 3 developed significant gonioscopic angle closure. These results suggest that asymptomatic partial angle closure was the cause of the observed changes and provide a naturally occurring model of one mechanism that can produce outflow damage without clinical symptoms.

There is no reason to suppose that acute, chronic, or intermittent closed-angle glaucoma is the only manifestation of angle closure in eyes at risk, and partial angle closure—without substantial changes in outflow or pressure—has been demonstrated in some (Mapstone, 1977a). There is therefore good reason to suppose that asymptomatic partial angle closure may occur spontaneously in some eyes, since the pressure increase can be small. It has also been shown that one episode of acute closed-angle glaucoma can leave an eye with a reduced facility of outflow, but the amount of damage is clinically insignificant, and the eye remains normotensive after an iridectomy (Mapstone, 1977b).

An eye at risk to the development of closed-angle glaucoma (because the fellow eye has had a spontaneous acute attack) is usually treated with a prophylactic peripheral iridectomy. There are other options. For example, it can be treated with miotics, or, if it does not develop a positive provocative test, may simply be observed. Since some of these eyes may develop spontaneous partial angle closure, it seems reasonable to suggest that they may, over the years, develop an increased pressure and outflow damage caused by a partial angle closing mechanism. This paper investigates that hypothesis.

Material and methods

The hospital records were searched for patients who had had acute closed-angle glaucoma in 1 eye and the fellow eye treated with prophylactic pilocarpine drops. The criteria for selection were: (1) Closed-angle glaucoma in 1 eye treated by surgery, the fellow eye treated with pilocarpine drops; (2) a minimum period of treatment with pilocarpine of 8 years; (3) no evidence that the pilocarpine-treated eye had ever developed intermittent or acute closed-angle glaucoma; and (4) a gonioscopically open angle with no peripheral anterior synechiae.

Twenty-two patients were found and two rejected because of peripheral anterior synechiae, that is, 20 patients were left for study.

The 20 patients were instructed to continue their pilocarpine drops as was their habit, and on the morning of test, at zero hours, intraocular pressures were measured and facility of outflow recorded. Then a pilocarpine-phenylephrine provocative test was done.

Another group of 20 eyes from 20 patients were then randomly selected from a larger group of 32 patients by the following criteria: (1) Closed-angle glaucoma in 1 eye treated by surgery, the fellow eye *not* treated and its behaviour studied prospectively; (2) a minimum follow-up period of 4 years; (3) no evidence that the untreated eye had ever developed spontaneous intermittent or acute closed-angle glaucoma or a positive provocative test; (4) a gonioscopically open angle with no peripheral anterior synechiae.

The 20 eyes on no treatment were then investigated as described above.

Finally, 20 patients were randomly selected from a group of 89 who had no evidence of glaucoma but had had a pilocarpine-phenylephrine provocative

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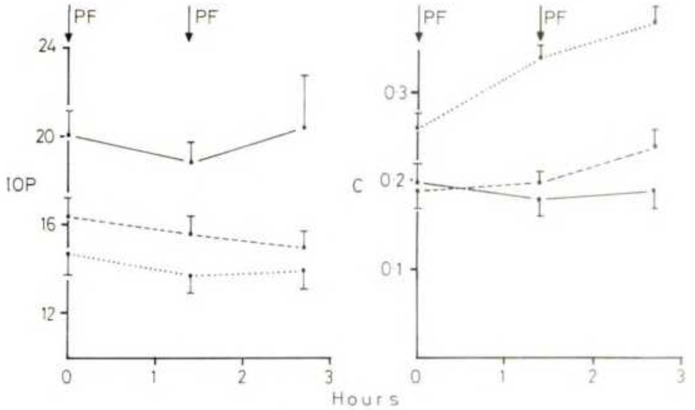

Fig. 1 *Result of a provocative test in 3 groups of eyes. Solid line: 20 eyes that had received prophylactic miotics for at least 8 years. Interrupted line: 20 fellow eyes at risk, on no treatment, and followed up for at least 4 years. Dotted line: 20 eyes with no evidence of glaucoma. Mean and standard error recorded. P = pilocarpine. F = phenylephrine*

test. The statistical test used was a Kruskal-Wallis one-way analysis of variance by ranks. Gonioscopy was done on every patient at the start and termination of the test.

Results

The mean intraocular pressure (Po), facility of outflow (C) and Po/C ratio for the 3 groups of eyes are shown in Table 1.

The first null hypothesis tested is that there is no significant difference in the mean intraocular pressure of the 3 samples. The calculated Kruskal-Wallis statistic was H = 43·6 and the probability of a value as large as this is <0·001. The null hypothesis is therefore rejected and the alternative hypothesis accepted—that is, the mean intraocular pressures of the 3 samples are so different that they cannot have been drawn from the same population.

The second null hypothesis tested is that there is no significant difference in the mean outflow facilities of the 3 samples. This again is rejected (H = 37·2, P<0·001), and the alternative hypothesis, that there is a difference, accepted.

Finally, the same result applies to Po/C ratios (H = 42·5, P<0·001).

The result of a provocative test in the 20 eyes on miotics is shown in Fig. 1. The first dose of pilocarpine and phenylephrine decreased pressure from a mean of 20·1 to 18·9 mmHg and decreased outflow from 0·2 to 0·19 μl mmHg/mm. The second dose increased pressure from a mean of 18·9 to 20·5 mmHg, and outflow changed from 0·18 to 0·19. Two patients developed acute closed-angle glaucoma and 16 gonioscopic closure of part of the angle during the test.

Table 1 *Mean intraocular pressure (Po), facility of outflow (C), and ratio Po/C for 3 groups of eyes*

	Miotics	*No treatment*	*Normals*
Po	20·1	16·4	14·6
C	0·198	0·187	0·259
Po/C	138·4	102·6	63·3

In the 20 contralateral eyes at risk on no treatment the result of a provocative test is shown in Fig. 1. The first dose of pilocarpine and phenylephrine decreased pressure from a mean of 16·4 to 15·7 mmHg, and outflow increased from 0·19 to 0·20. After the second dose pressure decreased from 15·7 to 15·0 mmHg, and outflow increased from 0·20 to 0·24. No eye developed a positive test, and in 15 gonioscopic closure of part of the angle occurred during the test.

Finally, in 20 normal eyes (Fig. 1) the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 14·5 to 13·7 mmHg, and outflow increased from a mean of 0·26 to 0·34. After the second dose pressure increased to 13·9 mmHg, and outflow to 0·38. No eye developed gonioscopic closure of any degree.

Discussion

At the start of the experiments all angles were open and free of peripheral anterior synechiae. There is no reason to suppose, nor evidence to suggest, that the outflow system in eyes at risk to the development of closed-angle glaucoma is abnormal. There is, therefore, every reason to suppose that—in the absence of angle closure—mean intraocular pressure and outflow facility in a sample of eyes at risk would not differ significantly from values obtained in a group of eyes in whom there was no evidence of glaucoma. The results show, however, that this null hypothesis must be rejected for pressure, outflow and Po/C ratios. What, then, is the explanation?

Firstly, it is possible that pilocarpine in some way damages the outflow system. The possibility must be allowed but is improbable, since in 20 eyes at risk that had received no miotics outflow at the start of the test was also reduced. Secondly, it could be argued that during tonography, in some narrow-angle eyes, the tonometer produces segmental iridocorneal contact and therefore low C readings. This may, of course, happen, but its significance is not immediately apparent. It would not, however, produce a significant pressure change.

The final possibility is that a raised pressure and outflow damage are a consequence of intermittent partial angle closure. There are two possibilities. (1) The mere apposition of iris to trabecular meshwork in some way damages the outflow system. This in turn produces a raised pressure. A priori this is an improbable explanation. (2) Intermittent partial angle closure produces an intermittently raised pressure which over the years is *the* cause of outflow damage. A potential vicious circle is generated which, once operating, no longer needs partial angle closure to sustain it.

The 20 eyes on long-term miotics all had narrow angles, and it is interesting that 80% developed partial angle closure but only 2 a positive provocative test with complete closure (normally 60 to 70% of eyes at risk develop a positive provocative test (Mapstone, 1976)). In the 20 fellow eyes on no treatment 75% developed partial angle closure and none a positive test.

The fact that in neither group had angle closure of any degree been seen—apart from during a provocative test—does not invalidate the argument. For if each angle is gonioscoped once a year and examined for 5 minutes that represents approximately 1 one-hundred-thousandth part of the year. It should occasion no surprise that partial angle closure had not been seen before a provocative test was done.

It is suggested, therefore, that the reduced outflow facilities in the eyes at risk are a consequence of intermittent partial angle closure, which, because it is partial, does not produce overt symptoms.

These observations have clinical implications, for they provide an explanation of one mechanism at work in some eyes with 'primary' ocular hypertension and open-angle glaucoma (Mapstone, 1978).

I thank Mrs E. Tubb for secretarial assistance.

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Mechanisms in ocular hypertension

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SUMMARY This paper investigates the hypothesis that intermittent partial angle closure is one of the causes of ocular hypertension. 139 eyes from 76 patients with ocular hypertension were provoked with pilocarpine and phenylephrine. Four distinct responses appeared. Firstly, in 39 eyes (from 24 patients, 32%) gonioscopic closure of part or all of the angle appeared. Secondly, in 30 eyes (from 19 patients, 25%) no angle closure occurred but there was a substantial pigment release into the aqueous. Thirdly, in 9 eyes (from 8 patients, 11%) both angle closure and pigment release occurred. Finally, in 61 eyes (from 36 patients, 59%) neither angle closure nor pigment release appeared. (Since the 2 eyes of a patient did not always behave in the same way, for example, 1 eye might develop angle closure and the other not, 1 patient may appear in 2 groups.) From the first group 1 eye from each patient was randomly chosen for iridectomy. A repeat provocative test at least 1 year later produced a significantly different result. It is considered that the evidence obtained in this study supports the hypothesis that intermittent partial angle closure is one of the causes of ocular hypertension.

There is no reason to suppose that ocular hypertension has one unique cause, and a clinically indistinguishable picture has been shown to occur in some eyes at risk to the development of closed-angle glaucoma (Mapstone, 1979a). This paper investigates the hypothesis that one of the causes of ocular hypertension is intermittent partial angle closure.

Material and methods

One hundred and thirty-nine eyes from 76 patients were studied. They were selected on the following criteria: (1) No story suggestive of intermittent closed-angle glaucoma; (2) no glaucomatous field defect; (3) a gonioscopically open angle with no peripheral anterior synechiae; (4) a mean applanation pressure on 3 consecutive occasions of 21 mmHg or more; (5) no anterior segment exfoliation; (6) no venous occlusive disease; (7) no family history of glaucoma.

The eyes were provoked as follows: At zero hour intraocular pressure was measured, facility of outflow recorded, and pilocarpine drops 2% plus phenylephrine drops 10% instilled. Approximately 1¼ hours from the start of the test the intraocular pressure was recorded, tonography was repeated, and another dose of pilocarpine and phenylephrine instilled. Finally, after another 1¼ hours (that is 2½ hours from the start of the test) pressure was recorded and tonography repeated.

Gonioscopy was done on *every* patient at the start and termination of the test. Thirty-three patients developed partial or complete gonioscopic closure of the angle in 1 or both eyes. One eye from each of these patients was then randomly selected for a peripheral iridectomy. The result of a provocative test before and *at least* 1 year after iridectomy are recorded (this represents 19 patients; in 14 cases 1 year has not yet elapsed since an iridectomy was done).

The critical measurement at the inception of angle closure is the distance between iris and cornea just internal to the limbus (Mapstone, 1979b). Angles were therefore divided into 3 groups: (1) Iridocorneal distance less than one-quarter of corneal thickness; (2) iridocorneal distance about one-quarter of corneal thickness; and (3) iridocorneal distance greater than one-quarter of corneal thickness. The gap was estimated in the temporal quadrant.

During each provocative test attention was also directed to the amount of pigment released into the aqueous and was subjectively classified as follows: (1) Pigment absent; (2) pigment present, but the

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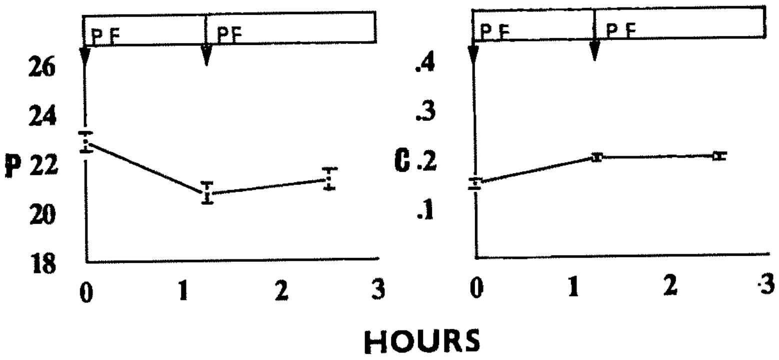
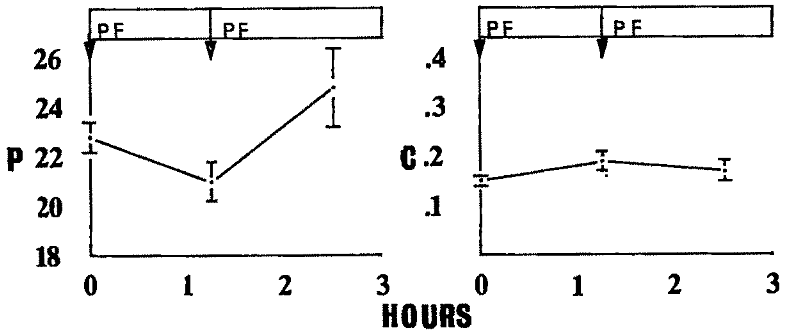


Fig. 1 *Response of 139 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded*

Fig. 2 *Response of 39 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded*



number of pigment granules present in a slit beam of 3 mm length could, if necessary, be counted; and (3) pigment present, but to such a degree that a count would be impossible.

Results

Provocative test result in 139 eyes from 76 patients

Fig. 1 records the mean response and shows that the first dose of phenylephrine and pilocarpine decreased pressure from a mean of 22·9 to 20·7 mmHg and increased outflow from a mean of 0·15 to 0·20 μl/mmHg per min. The second dose increased pressure from a mean of 20·7 to 21·3 mmHg, outflow remained at 0·20.

The 4 patterns of outflow response described previously (Mapstone, 1977a, b, 1978) were also shown by this group. However, for the purpose of this paper the responses are analysed as follows.

(1) Response of 39 eyes (from 27 patients) that developed gonioscopic angle closure only. Fig. 2 records the result and shows that the first dose of pilocarpine and phenylephrine reduced pressure from a mean of 22·7 to 21·1 mmHg and increased outflow from a mean of 0·15 to 0·19. The second dose increased pressure from a mean of 21·1 to 24·7 mmHg and outflow decreased from a mean of 0·19 to 0·17.

The statistics of this group are, however, biased by the fact that 8 eyes from 6 patients developed acute closed-angle glaucoma (gonioscopic closure with an increase in pressure of at least 8 mmHg) during the test. In 8 eyes reductions in pressure and substantial increases in outflow occurred in spite of extensive gonioscopic closure. This fact is obscured by the analysis.

(2) Response of 30 eyes (from 19 patients) that developed no gonioscopic angle closure but released much pigment into the aqueous. Fig. 3 records the result and shows that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 22·9 to 21·2 mmHg and increased outflow from a mean of 0·16 to 0·17. The second dose increased pressure from a mean of 21·1 to 21·9 mmHg and outflow decreased from a mean of 0·17 to 0·16.

(3) Response of 9 eyes (from 8 patients) that developed both gonioscopic angle closure and much pigment release. Fig. 4 records the result and shows

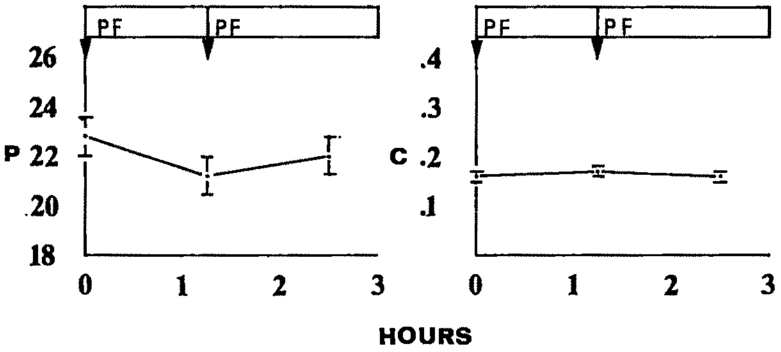


Fig. 3 *Response of 30 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded*

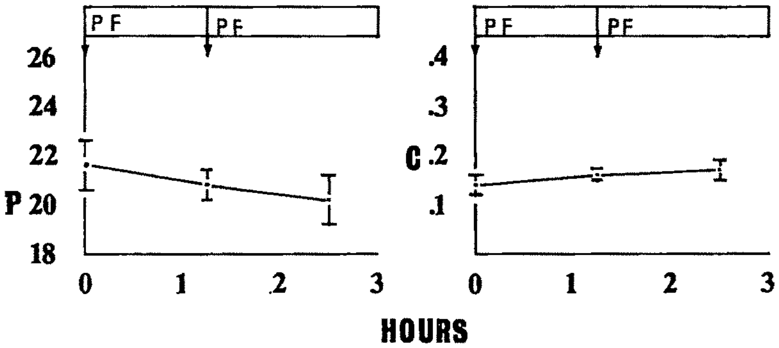


Fig. 4 *Response of 9 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded*

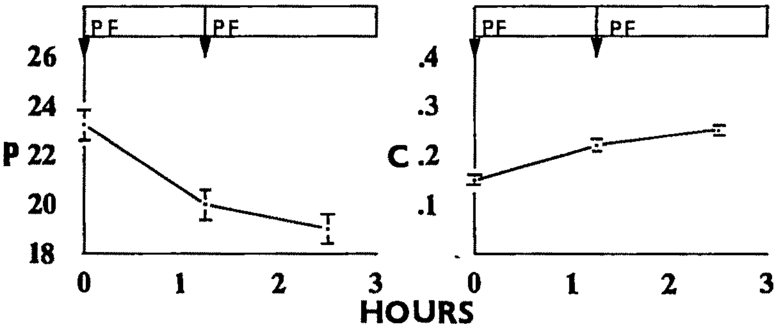


Fig. 5 *Response of 61 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded*

that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 21·6 to 20·8 mmHg and increased outflow from a mean of 0·14 to 0·16. The second dose decreased pressure from a mean of 20·8 to 20·2 mmHg and increased outflow from a mean of 0·16 to 0·17. No patient developed acute closed-angle glaucoma.

(4) Response of 61 eyes (from 36 patients) that developed neither gonioscopic angle closure nor pigment release. Fig. 5 records the results and shows that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 23·3 to 20 mmHg and increased outflow from a mean of 0·15 to 0·22. The second dose decreased pressure from 20 to 19·1 mmHg and increased outflow from 0·22 to 0·25.

An analysis of the overall change in pressure and facility of outflow produced by a provocative test in the different groups is shown in Table 1. It can

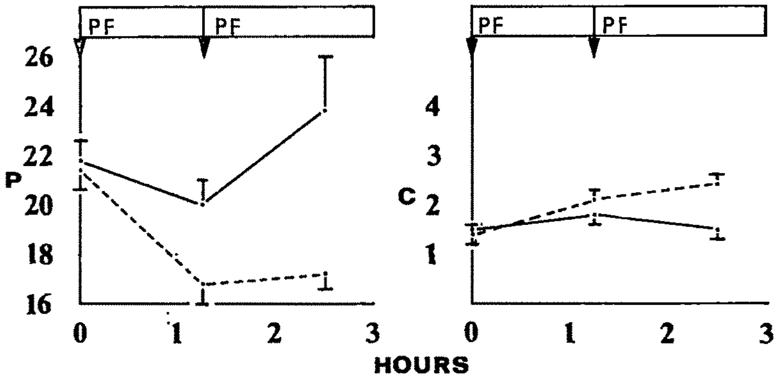


Fig. 6 *Response of 19 eyes to provocative testing with pilocarpine (P) and phenylephrine (F), before (solid line) and after (interrupted line) a peripheral iridectomy. Mean and standard error recorded*

Table 1 *Significance of the changes in pressure and outflow in various groups of eyes during a provocative test*

	Δ*P*		Δ*C*	
	t	*P*	t	*P*
AC only	1·06	NS	1·45	NS
PR only	1·02	NS	0·36	NS
AC + PR	1·31	NS	1·63	NS
Neither	6·16	<0·001	7·91	<0·001
All eyes	2·52	<0·02	6·09	<0·001

AC = angle closure. PR = pigment release. *t* = Student's *t* statistic. P = probability value. ΔP = total change in pressure. ΔC = total change in outflow. NS = not significant

be seen that in eyes showing angle closure, pigment release, or both no significant change in pressure or outflow occurred. In the 61 eyes that showed neither there was in contrast a very significant decrease in pressure and increase in outflow.

Provocative test result in 19 eyes before and after a peripheral iridectomy

Before iridectomy: Fig. 6 records the mean response and shows that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 21·8 to 20·1 mmHg and increased outflow from a mean of 0·15 to 0·18. The second dose increased pressure from a mean of 20·1 to 23·8 mmHg, and decreased outflow from a mean of 0·18 to 0·15. Neither the overall change in pressure nor outflow was statistically significant.

After iridectomy: Fig. 6 records the mean response and shows that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 21·4 to 16·9 mmHg and increased outflow from a mean of 0·14 to 0·21. The second dose increased pressure from a mean of 16·9 to 17·1 mmHg and increased outflow from 0·21 to 0·24. Both the overall decrease in pressure and increase in outflow are statistically significant (P<0·001). None developed angle closure of any degree.

Incidence of angle closure in eyes graded according to iridocorneal distance

Table 2 records the result and shows that there is a significant association between iridocorneal distance and the subsequent development of angle closure.

Discussion

The results described show that, analysed as a group, the 139 eyes responded to a provocative test in a way similar to normal eyes, showing a significant decrease in pressure and increase in outflow (Mapstone, 1977c). This result is due to the fact that 61 (44%) of the eyes developed neither angle closure nor pigment release (Fig. 5). In the 3 groups that did, a provocative test produced no significant change in either pressure or outflow, and the evidence suggests that this is a direct consequence of angle closure or pigment release. This is confirmed in 19 randomly chosen eyes that developed angle closure, since after a peripheral iridectomy a repeat provoca-

Table 2 *Incidence of gonioscopic angle closure in eyes with varying iridocorneal distances*

	Iridocorneal distance		
	<¼	¼	>¼
Number of patients	8	32	36
Number with angle closure	7	22	4
	(88%)	(69%)	(11%)

¼ = One-quarter of corneal thickness

tive test produced a highly significant pressure decrease and outflow increase (Fig. 6).

The results show that in 40 to 45% of patients with ocular hypertension gonioscopic closure of all or part of the angle can be seen on provocative testing. This may be merely an association signifying nothing in particular. However, gonioscopic angle closure is a rare event in nonglaucomatous eyes randomly selected for provocative testing (Mapstone, 1977c) but occurred in 53% of a group of normal eyes selected because of a gonioscopically narrow angle (Mapstone, in preparation). So the alternative explanation—that there is a causal relationship—is therefore worth examining.

In order to do this it is necessary to erect a hypothesis to explain the putative relationship and from this derive implications that can be submitted to experimental test. The first hypothesis is that ocular hypertension causes angle closure. This is, a priori, highly improbable and will not be discussed. The second hypothesis follows.

Angle closure is not an all-or-none phenomenon, but rather eyes exist in which some of the angle is closed for some of the time only. Eyes showing this progress through the following stages: *Stage 1* represents an eye that develops intermittent partial angle closure and, because of this, an intermittently raised pressure. After an (undetermined) interval the cumulative effect is *Stage 2*. An intermittently raised pressure then produces damage to the outflow system which shows as a reduced facility of outflow. The affected eye now has a permanently raised pressure and outflow damage—that is, ocular hypertension (Fig. 7).

A situation has been created which can evolve in one of several ways: (1) The trigger mechanism (intermittent angle closure) ceases to operate and the eye is left with ocular hypertension; (2) the mechanism continues to operate intermittently but at no point does a sufficient increase in pressure occur to produce a field defect—that is, ocular hypertension persists; (3) eventually pressure rises sufficiently to produce a field defect and the eye passes to *stage 3*, the stage of open-angle glaucoma.

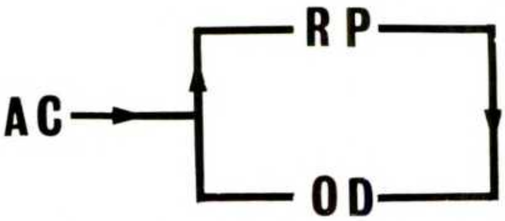


Fig. 7 *Postulated mechanism for the aetiology of ocular hypertension. Intermittent angle closure (AC) produces a raised pressure (RP) which, in turn, is the cause of outflow damage (OD)*

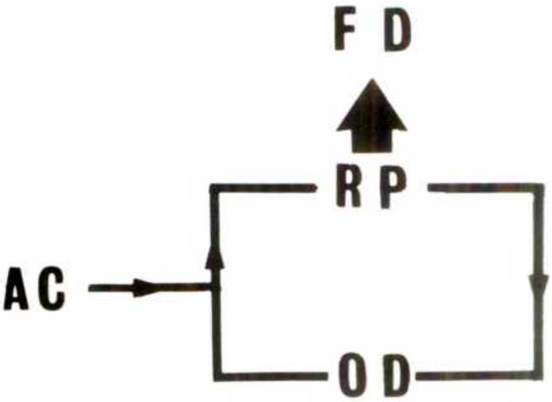


Fig. 8 *When pressure has increased sufficiently a field defect (FD) appears and the eye passes to the stage of open-angle glaucoma*

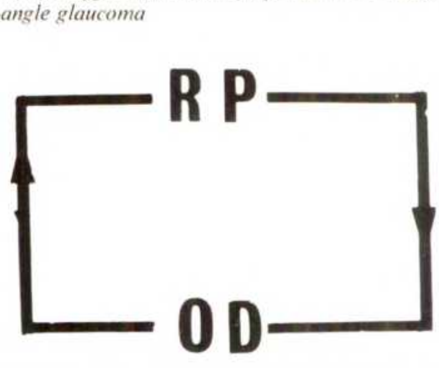


Fig. 9 *A stage is reached in some eyes where a trigger mechanism is no longer necessary. Here a raised pressure (RP) has produced outflow damage (OD) which raises pressure more, and a self-perpetuating mechanism is generated*

There are two ways in which this can be achieved. Firstly, intermittent angle closure increases an already raised pressure sufficiently to produce a field defect (Fig. 8). Secondly, an increased pressure (the result of intermittent partial angle closure) may damage the outflow system so much that that damage increases pressure still more. This in turn produces more outflow damage, and the self-perpetuating mechanism shown in Fig. 9 is generated. It no longer needs a trigger mechanism to sustain it and alone produces a field defect.

A number of implications can be derived from this hypothesis and submitted to experimental test. They are as follows:

(1) If the hypothesis is correct, then intermittent partial angle closure occurs and produces a raised pressure with no clinical symptoms. The evidence

for partial angle closure has been described in this paper and elsewhere (Mapstone, 1977a). That it may be intermittent can be inferred from the behaviour of contralateral eyes at risk to the development of closed-angle glaucoma that do not have a peripheral iridectomy (Mapstone, 1979a).

(2) A raised pressure produces permanent outflow damage. Evidence for this comes from several sources. It is a common clinical observation that after an episode of acute closed-angle glaucoma and subsequent iridectomy some eyes still need treatment to maintain a clinically acceptable pressure. Whatever the proximate causes of the underlying outflow damage may be, the remote cause is a raised pressure. Again, even in eyes that are normotensive after an acute attack, outflow damage can be demonstrated relative to the contralateral eye (which has not had a spontaneous acute attack) (Mapstone, 1977d).

(3) Partial angle closure produces ocular hypertension. Eyes at risk to closed-angle glaucoma (because the fellow eye had had an acute attack) may be treated with prophylactic pilocarpine drops. After a period of years a raised pressure and reduced facility of outflow may appear, although the angle is open, free of peripheral anterior synechiae, and there is no clinical evidence to suggest that acute chronic or intermittent closed-angle glaucoma has occurred. Since 90% of these eyes developed angle closure of some degree on provocative testing the reasonable inference is that intermittent partial angle closure has produced a picture clinically indistinguishable from ocular hypertension (Mapstone, 1979a). To say that this is a secondary change—which it is—and therefore not comparable to the change in 'primary' ocular hypertension begs the question.

(4) Another test implication is that if most instances of open-angle glaucoma are preceded for a variable period by ocular hypertension, then partial angle closure should be demonstrable in some eyes with open-angle glaucoma. Evidence for this has been published (Mapstone, 1978).

(5) Finally, if angle closure could be demonstrated in the ocular hypertension or open-angle glaucoma associated with venous occlusive disease, anterior segment exfoliation or diabetes then that would be additional supportive evidence for the hypothesis. There is evidence that this is so (Mapstone, in preparation).

The value of a hypothesis is directly proportional to the number of implications that can be derived from it and verified experimentally. It is suggested that there is now sufficient reason to suppose that an angle-closing mechanism is *one* of the causes of 'primary' ocular hypertension and open-angle glaucoma.

One other point is of interest. Published data (Armaly, 1969; Perkins, 1973; Wilensky *et al.*, 1974; Kitazawa *et al.*, 1977) suggest that 10% of patients with ocular hypertension proceed to open-angle glaucoma. It therefore necessarily follows that the majority of ocular hypertensives with partial angle closure will not develop field loss. There is therefore not sufficient reason for doing a peripheral iridectomy in all hypertensives with demonstrated angle closure, neither is there, at the moment, evidence to show which should be chosen. One thing is clear, ocular hypertension, partial angle closure, and a reduced outflow facility are quite compatible with normal visual health.

The results too have implications for gonioscopy as currently practised. It has already been shown that gonioscopic angle closure does not necessarily imply true angle closure (Mapstone, 1979b). It also follows from the results described above that from the coincidence of a raised pressure and open angle it cannot be asserted that the cause of the raised pressure (proximate or remote) is not angle closure. The fact that patients with non-narrow angles developed partial angle closure is also of significance. Finally, pigment release prevents (Fig. 3) the expected decrease in pressure and increase in outflow on provocative test and suggests that this may be another model of outflow damage. These points are explored in subsequent papers.

I thank colleagues who referred patients for study and Mrs E. Tubb for secretarial help.

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Anterior membrane dystrophy following cataract extraction

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SUMMARY This paper describes a patient with previously normal corneas who underwent bilateral cataract surgery. This was followed by acute dehiscence of the epithelium and the eventual appearance of fingerprint lines, microcysts, and map-like areas typical of Cogan's microcystic dystrophy. Light and electron microscopy showed the presence of epithelial microcysts and a seam of subepithelial material like basement membrane. It is suggested that this patient represents a rapid transition from apparent normality to an extensive anterior membrane dystrophy, precipitated by operation for cataract.

A unique corneal complication of cataract surgery is presented in this paper, which describes the bilateral acute onset of an anterior membrane dystrophy. Fingerprint lines of the cornea were first described by Guerry as fine wavy lines with whorl-like contours located within the corneal epithelium and best seen by retroillumination (Guerry, 1950). He noted similar lines in keratoconus and advanced Fuchs's dystrophy. His clinical observations were confirmed and supplemented by subsequent authors, who demonstrated histologically a splitting of Bowman's membrane (DeVoe, 1962; Kaufman and Clowers, 1966). Recent authors have included finger-print, net, and bleb dystrophies with Cogan's microcystic dystrophy (Cogan *et al.*, 1964) in a complex of interrelated superficial corneal disorders, the anterior membrane dystrophies (Bron and Brown, 1971; Trobe and Laibson, 1972). It has been suggested that anomalies of the basement membrane are the prime cause of both the fingerprint lines and the epithelial microcysts (Cogan *et al.*, 1974; Rodrigues *et al.*, 1974).

Fingerprint striae have recently been described both as an idiopathic dystrophic form (Brodrick *et al.*, 1974*a*) and as an accompaniment of herpes simplex keratitis (Brodrick *et al.*, 1976). There is only one previous report of the condition occurring in an aphakic patient (Rodrigues *et al.*, 1974), but no mention has been made of the explosive onset and progressive course seen in the case discussed here. This contrasts with a recent report of 5 patients with Cogan's microcystic dystrophy who had intraocular surgery without any unfavourable effects except for mild progression in one patient (Luxenberg *et al.*, 1975).

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Case report

A 62-year-old Caucasian woman with no previous history of ocular or general disease was first seen in 1970 with failing vision due to bilateral cataracts. Corneal examination at that time was normal. By 1972 her vision had deteriorated considerably and lens extraction was recommended. Apart from the cataracts, preoperative examination of her eyes revealed no other abnormality.

In September 1972 a routine intracapsular lens extraction was carried out with an uneventful postoperative period. Three weeks later she developed a sensation of a foreign body in the left eye which rapidly became intensely painful, accompanied by extreme photophobia and lacrimation. Examination showed swelling of the left eyelids, intense blepharospasm, and profuse tearing. There was marked conjunctival hyperaemia, and the left cornea appeared hazy.

Slit-lamp examination showed that the lower half of the cornea was covered by circumferential whorls which closely resembled a thumbprint (Fig. 1). At high magnification these whorls were seen to consist of multiple small ridges in oedematous epithelium which was heaped up into folds. Moreover the whole of the affected area was slightly mobile and was dehiscing from the underlying basal lamina and stroma. No staining was noted, but the tear film was broken up by the epithelial ridges. Bowman's

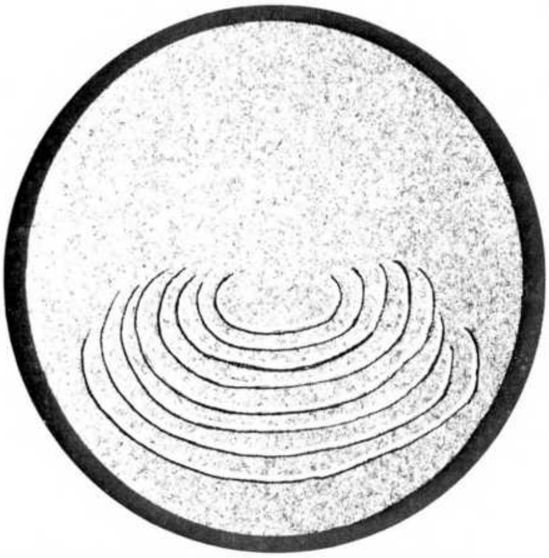

Fig. 1 *Drawing of cornea to illustrate the overall distribution of the epithelial whorls*

layer appeared normal, and there was no evidence of stromal oedema. The stroma measured 0·5 mm with a normal endothelium and Descemet's membrane. The anterior chamber showed no significant flare or cells and the vitreous face was intact and well back. Intraocular pressure was 18 mmHg by applanation tonometry. Corneal sensation was greatly reduced.

Treatment was continued with atropine and corticosteroid drops and admission was arranged for epithelial debridement 3 days later. In this short time, however, all striae and affected epithelium were shed and her symptoms completely abated. Biomicroscopy now showed that the whorls had been replaced by scattered epithelial microcysts and greyish map-like areas consistent with the diagnosis of Cogan's microcystic dystrophy (Fig. 2). The cornea was otherwise normal apart from the decreased sensation.

Since then she has experienced intermittent episodes of discomfort and foreign body sensation, particularly on awakening in the morning, tending to alleviate as the day progressed. By January 1973 in addition to the features of Cogan's microcystic dystrophy some fine fingerprint striae had appeared in the nasal periphery (Fig. 3). Throughout this period the right cornea was entirely normal to clinical examination.

In May 1973 an uncomplicated intracapsular lens extraction was performed on the right eye with an uneventful postoperative period. Twelve weeks afterwards severe pain and discomfort developed in the right eye. Examination revealed swelling of the lids, intense blepharospasm, lacrimation, and photophobia. The conjunctiva was hyperaemic and the lower half of the cornea appeared hazy. Slit-lamp examination showed that the upper half of the cornea was normal; the lower half was oedematous and heaped up into striae, the appearances being identical to those previously seen in the left cornea. The epithelium was extremely mobile, and, as in the left cornea, though no stain was present the tear film was broken up by the epithelial striae. Corneal sensation was reduced. There was no apparent abnormality of Bowman's layer, the

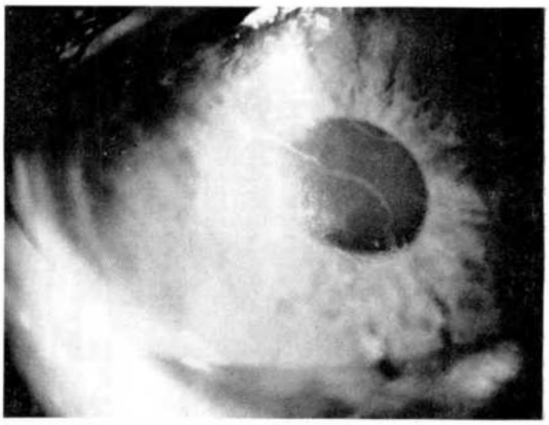

Fig. 2 *Photograph of cornea showing the large map-like areas in the centre* (× 1)

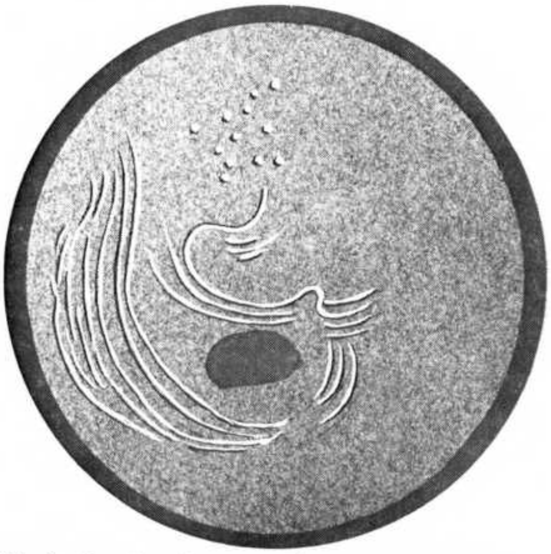

Fig. 3 *Drawing of cornea to illustrate the distribution of map-like areas, fingerprint striae, and microcysts*

stroma, Descemet's membrane, or the endothelium.

The anterior chamber was quiet, the vitreous face intact and well back, and the intraocular pressure was 19 mmHg by application tonometry. The affected epithelium was removed immediately under topical anaesthesia. The specimen was divided into 2; one half was fixed in formalin and embedded in paraffin for conventional microscopy, the other half was fixed in cold 2·5% gluteraldehyde, washed, and postfixed in 1% osmium tetroxide and embedded in Araldite for electron microscopy.

Her subsequent progress has been satisfactory, with a corrected vision of 20/25 in each eye. She still has intermittent attacks of discomfort and a foreign body sensation affecting both eyes, usually when she wakes in the morning. They tend to improve as the day progresses. There have been no further attacks of intense pain.

Examination in 1974 showed the following corneal appearances. In the right central cornea a greyish, map-like area with fine linear borders was visible, lying in the deep aspect of the epithelium. Some fine fingerprint striae were seen in the upper nasal and lower temporal periphery, and scattered epithelial microcysts were evident both centrally and peripherally. The microcysts and fingerprint striae were best seen by retroillumination and showed reverse illumination, denoting increased optical density of their contents (Graves, 1924). The left cornea showed numerous whorled fingerprint striae mainly in the nasal half of the cornea. Some scattered epithelial microcysts were observed in the supranasal quadrant, and a greyish map-like area could be seen just below the centre of the cornea. The striae and microcysts were best seen by retroillumination and showed reverse illumination as in the right eye. Schirmer's test with local anaesthesia revealed decreased lacrimal secretion, 4 mm in 5 minutes in the right eye, 3 mm in 5 minutes in the left eye. The tear film showed break-up over the area of the fingerprint striae, so that linear dry zones rapidly became apparent. The anterior corneal mosaic was interrupted in the areas of the epithelial changes. The microcysts showed no affinity for fluorescein. Corneal sensation assessed with monofilament silk of varying calibre was normal. In both eyes the corneal stroma was normal, with no visible abnormality of Bowman's layer, Descemet's membrane, or the endothelium. The anterior chambers were deep and quiet, the vitreous face intact and well back, and intraocular pressure 19 mmHg by applanation tonometry.

LIGHT MICROSCOPY

The specimen comprised epithelium, basal lamina, and some superficial stromal lamellae. The epithelium showed the normal 5-layered structure. The cellular morphology was essentially normal, with no evidence of pleomorphism, acanthosis, or acantholysis. There was no dysplasia, but scattered areas of spongiosis were noted. Epithelial microcysts of varying shape and size were located at different levels (Fig. 4). In some areas pale staining basal cells were observed. The microcysts contained a mixture of intensely basophilic coarse granules and a pale blue, finely granular substance. The nuclei were pyknotic, and the intercellular debris was characteristic of degenerating epithelial cells.

A thin seam of moderately basophilic, homogeneous material was present deep to the apparently normal basal lamina. In some sections small projections from this seam appeared to intrude into the epithelium. The subepithelial material was periodic acid Schiff negative (Fig. 5).

ELECTRON MICROSCOPY

The epithelial microcysts presented a typical appearance with microvillous projections into a cavity containing a variety of degenerating organelles and nuclear material (Fig. 6). The subepithelial seam consisted of a matrix of closely-packed granules 80 Å in diameter containing randomly interspersed fibrillae 170 Å (17 nm) in width, banded at 125-Å intervals. In some areas this seam projected up into the epithelium. The basement membrane and Bowman's layer were of normal thickness and contour and the superficial stromal lamellae were normal.

Discussion

This case is of interest because it represents a transition from a clinically normal asymptomatic

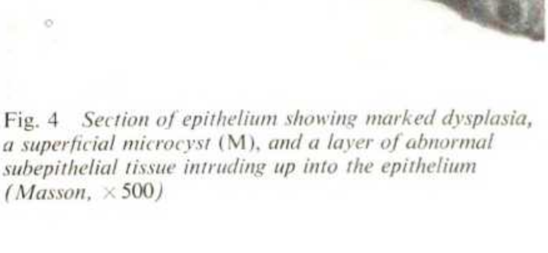

Fig. 4 *Section of epithelium showing marked dysplasia, a superficial microcyst* (M), *and a layer of abnormal subepithelial tissue intruding up into the epithelium (Masson,* × 500*)*

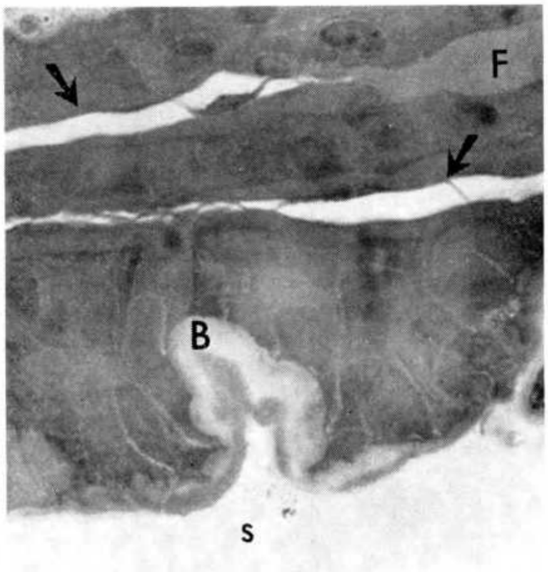

Fig. 5 *Section of epithelium showing subepithelial seam of abnormal tissue* (S) *invaginating the grossly thickened basement membrane* (B) *up into the epithelium. Clear spaces (arrowed) are artefacts, but possibly represent a plane of cleavage caused by fingerprint line* (F) (*Masson*, × 1750)

cornea through an acute episode of epithelial dehiscence to an established anterior membrane dystrophy of the Cogan's microcystic and fingerprint variety.

Epithelial microcysts are a feature of many corneal disorders, including the recurrent erosion syndrome (Tripathi and Bron, 1972), Meesman's epithelial dystrophy (Kuwabara and Cicarelli, 1964), and Cogan's microcystic dystrophy (Guerry, 1965). Their presence has also been noted in a complex of interrelated superficial corneal disorders (Bron and Brown, 1971) now regarded as a distinct group, the anterior membrane dystrophies. The microcysts described in these various conditions appear histologically identical (Rodrigues *et al.*, 1974; Brodrick *et al.*, 1974, 1976). Although the precise mechanism of the microcyst formation is still in dispute, several theories exist to account for it, including the inhibited migration theory of Cogan *et al.* (1974) and the inverted basal cell theory of Rodrigues (Rodrigues *et al.*, 1974). They may, however, represent a much more basic entity (Brodrick *et al.*, 1974), and it would seem reasonable to suggest that the cornea, whose unique and fundamental property is its transparency, has by virtue of its avascular nature only a limited number of inherent pathological responses. It has been suggested that the microcyst reaction represents a process whereby the corneal epithelium secludes and deletes degenerating cells, a type of epithelial phagocytosis, although a true phagosome is probably not formed (Brodrick *et al.*, 1974).

The seam of subepithelial material which probably results from disordered metabolism of the basal epithelial cells readily explains the defective epithelial adhesion. A similar seam has been documented as the basis of fingerprint dystrophy (Brodrick *et al.*, 1974).

It has frequently been commented that the superficial corneal disorders represent a broad spectrum of probably interrelated disorders, and a search has been made for a common pathogenesis which may not, however, exist. It is more probable that a variety of aetiological agents, including a true dystrophic process in the basal cells, can pursue a final common path to produce a similar ultrastructural and clinical appearance.

The importance of the present case is that it represents a rapid evolution, probably precipitated by surgery, from clinically normal cornea to the typical appearances of Cogan's microcystic dystrophy with fingerprint lines. The intermediate phase of acute epithelial dehiscence is similar to the

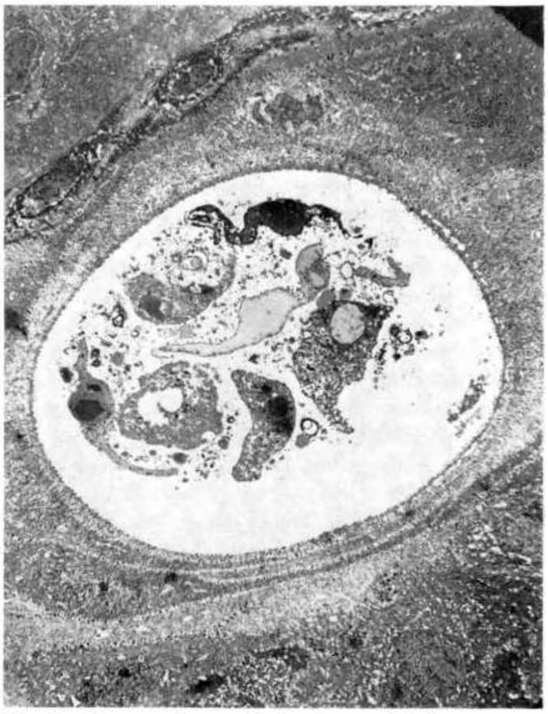

Fig. 6 *Electronmicrograph showing epithelial microcyst with microvillous lining and degenerating cellular debris in the cyst cavity (uranyl acetate and lead citrate,* × 800)

superficial linear keratitis described by Spicer and Greeves (1916). An unusual feature was the localisation entirely in the lower half of each cornea. One might have expected these changes to occur in the upper half adjacent to the cataract incision, where the effects of surgical trauma and the interference with nutrition and sensation would be maximal. It is difficult to explain this distribution.

This case, apart from its unusual features, adds further support to the concept that a series of dissimilar epithelial reactions may be transitional states in a spectrum of related disorders. The fundamental disorder common to the group is probably a disturbance in the metabolism of the basal epithelial cells. This results in the formation of the subepithelial material responsible for epithelial adhesion problems and fingerprint lines and triggers off the formation of microcysts, enabling the cornea to degrade and extrude degenerating and damaged cells by a process which does not prejudice its normal avascularity and transparency.

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Punctiform and polychromatic pre-Descemet's dominant corneal dystrophy

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SUMMARY A new type of pre-Descemet's corneal dystrophy is described. The opacities are punctiform, polychromatic, of uniform size, and evenly distributed over the whole cornea. The diagnosis is made only by slit lamp because there is no visual impairment. The disease is hereditary and follows the autosomal mode of inheritance with a high percentage of penetrance, expressivity, and specificity in 4 successive generations, in which 8 affected members were observed among a total of 46.

The purpose of this paper is to present a clinical form of corneal dystrophy with pre-Descemet's localisation, familial character, and dominant heredity. We observed first this corneal dystrophy in a routine test on a woman aged 36 who presented with slight myopia. The deep polychromatic opacities seen by the slit lamp called it to our attention. We were then able to examine 46 members of her family and found the same corneal feature in 8 of them. Without exception this corneal dystrophy did not interfere with visual acuity. Because of its clinical and biomicroscopical characteristics and its localisation we include it in the group of the so-called pre-Descemet's corneal dystrophies, classified topographically by François (1966).

After reviewing the literature on the corneal pathology we considered our cases showed a special type of dystrophy that had not been reported previously. There was no backward indentation on Descemet's membrane nor endothelial abnormalities (Thomsitt and Bron, 1975) so far as we could judge from slit-lamp examination. We showed Professor Jules François one of these cases, and he agreed that it represented a unique clinical form and was the more interesting because of its hereditary character.

Vogt (1923) was the first to describe a pre-Descemet's dystrophy, which he called cornea farinata. In this paper we refer only to pre-Descemet's dystrophies. Paufique and Etienne (1950) reported a family trait in the senile and presenile forms. Maeder and Danis (1947) described a deep filiform dystrophy of the cornea associated with keratoconus. Later, Franceschetti *et al.* (1957) demonstrated that this dystrophy is not necessarily associated with keratoconus. Franceschetti and Maeder (1954) described a case of deep punctiform dystrophy associated with ichthyosis. Then Franceschetti and Schlaeppi (1957) presented a case of pre-Descemet's dystrophy with ichthyosis and band-shaped degeneration.

Collier (1963) made a comparative study of all these cases, establishing an order and classifying them as pre-Descemet's dystrophies. It should be emphasised that neither the ichthyosis nor the keratoconus are necessary associations of these dystrophies. The same author rather vaguely indicates its familial and hereditary character.

Grayson and Wilbrandt (1967) proposed a new classification based on the shape of the opacities. Curran *et al.* (1974), in a histopathological study of a pre-Descemet's corneal dystrophy, found enlarged keratocytes with intracytoplasmatic vacuoles containing a lipofuscin-like lipoprotein. They considered this process to be related to age. Fiore and Regamey-Steiger (1975) described the association of a dominant autosomal ichthyosis and a corneal pre-Descemet's dystrophy of a deep punctiform type.

One of us (Malbran, 1972), studying the family of a typical case of macular dystrophy of Groenouw, found that a cousin of the propositus presented a pre-Descemet's dystrophy that was then classified as filiform and by its morphological characteristics and its distribution was similar to the one we are presenting in this report.

Case report

First generation. A couple from the French Pyrenees established themselves in Buenos Aires in the 19th century. Their descendants were:

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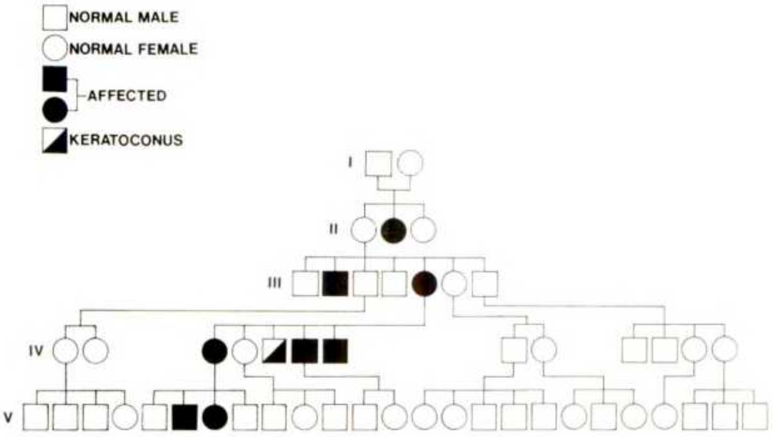

Fig. 1 *Family tree showing the dominant autosomal heredity of the punctiform and polychromatic pre-Descemet's corneal dystrophy*

Second generation. Three daughters. One of these died without her descendants being examined. The second was single and had no offspring; she was examined when she was 87 years old, 2 weeks before her death. She suffered from the dystrophy reported here. The third sister married a native Argentian of Austro-Hungarian origin and is the mother of the third generation, consisting of 7 members.

Third generation. Five men and 2 women. They were all examined, and 2 of them showed the dystrophy. One, a single man of 68, without descendants, did not present any other ocular disease. The other, a woman of 62, married and had 5 children.

Fourth generation. Three men and 2 women. As in the third generation, all the 13 members were examined and the dystrophy was found in 3 of them. A fourth person, a man of 33, has keratoconus and is slightly myopic but suffers no dystrophy. Of the 3 who have the dystrophy 1 is a 31-year-old single man with no descendants so far, slightly myopic. The second is a married man of 32 with a son and daughter. The children have no dystrophy. The third is a woman of 36, with 4 children.

Fifth generation. All 25 members of this generation have been examined, and only 2 of them present the dystrophy. One is a boy of 5 years and the other a girl of 3.

In the course of this research we have seen all the living members of this family. In all, 46 people were examined. At present all members of the third and fourth generations are alive.

Discussion

A comparison of previous reports of pre-Descemet's dystrophies with the study we are now presenting shows the following differences.

Cornea farinata. Greyish, punctiform, and very thin elements and wavy lines with the form of a coma. Invisible to indirect illumination.. Distributed throughout the cornea except at the periphery.

Deep filiform dystrophy. Filaments in curls and sometimes punctiform. They are white to direct illumination and bluish grey to indirect illumination. Generally of central location and sometimes paracentral.

Deep punctiform dystrophy. Punctiform elements that are present in small groups of filaments, some of which are of a dendritic type, and others like canes or comas. Bluish white colour. Visible to direct and indirect illumination. Ring or strictly axial distribution of the opacities.

Polychromatic dystrophy. Thin punctiform elements that show different colours. Visible to direct and indirect illumination. Distributed all over the cornea up to the limbo without leaving free spaces.

All these dystrophies as well as the type we are presenting are similar in their essential features, but they differ completely in colour, since this dystrophy is the only one that presents a variety of colour that is constant in both types of illumination. Moreover, the distribution differs, because it is uniform throughout the whole cornea.

Another distinct slit-lamp feature of this dystrophy is the presence of some polychromatic opacities leaving empty, clear spaces larger than the opacities themselves. These opacities are punctiform and have polychromatic reflections, some are yellow, others are greenish, and others are red. Their size is more or less uniform, as is their topographical distribution, which covers the whole corneal diameter at the pre-Descemet's depth. There is a slight decrease in number at the extreme periphery, and they are not aggregated in any particular formations.

This entity can be seen only with the slit lamp with direct and indirect illumination. We would emphasise that the opacities are of equal size, being larger than those of the farinata. The dystrophy entity can be diagnosed only with the slit lamp. It does not evolve with time, nor does it change with the patient's age.

From studying the family tree we deduce that the pre-Descemet's dystrophy in this case is hereditary. The disease has been transmitted as an autosomal dominant way. This type of heredity is designated because the disease was present in 4 successive generations, about 50% of affected members having the trait without sex predilection.

Other characteristics of hereditary diseases are present: homochronicity, that is, the appearance of the illness at the same age among different members, and homology and homotypy, that is, the repetition of the illness and the same symptoms in the different members of the same family group.

The gene appears to show a high degree of penetrance, with similar phenotypic expression in different members of the family. Moreover, this corneal disease shows besides its familial character other typical signs that permit its identification as corneal dystrophy. These are bilaterality and symmetry, absence of neovascularisation, congenital or early onset, and no evolution.

The clinical and biomicroscopical aspect of our cases leads us to regard it as a new dystrophy. Nevertheless, we must point out its relation to other pre-Descemet's dystrophies.

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Changes in refraction between the ages of 1 and 3½ years

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SUMMARY A study has been made of the changes in refraction as a sample of 148 children grew between the ages of 1 and 3½ years. There was no decrease in hypermetropia, but there was a significant decrease in the incidence of astigmatism. Study of the changes in the refraction in the horizontal and vertical meridia of individual eyes gave clear evidence of a trend towards emmetropia if the initial refraction in either meridian was myopic or less than +2·50 D. Above that level the refraction became more or less hypermetropic.

A knowledge of the changes that take place in the refraction of children during and after the sensitive period is required if we are to understand any connection between refractive errors and squint and amblyopia. Lagleyze (in Lyle, 1950) believed that there was a steady decrease in hypermetropia after birth, but Fabian (1966) has suggested that a process of 'emmetropisation' occurred. So far the only study of the changes of refractions occurring in a sample of children as they grow was confined to children over the age of 3 years (Sorsby *et al.*, 1961).

The old-established view, attributed to Lagleyze (in Lyle, 1950) is that all babies are born hypermetropic and as they grow they become less long-sighted. This view has been criticised by Cook and Glasscock (1951) and Ruskell (1967). Recent observations show that newborn babies are not predominantly hypermetropic (Cook and Glasscock, 1951; Graham and Gray, 1963; Grignolo and Rivara, 1968; Gotch and Kitazawa, 1968; Goldschmidt, 1969; Patel *et al.*, 1970; Lledo, 1976). Such a hypothesis would be confirmed if there was a decreasing incidence of a given level of hypermetropia or if the mean of the range of refractions shifted towards myopia. On the other hand Fabian (1966), relating his own observations in children during the second year of life to other workers' reports of refractions of children at different ages, observed that a curve drawn to represent the refractions of newborn children had a very wide spread and that this variation decreased as the age of the children increased. This suggests that there is a tendency for those children born either myopic or hypermetropic to become emmetropic. So far Fabian's hypothesis has not been challenged.

Materials and methods

Details of the 148 children and their refractions at ages 1 and 3½ years have been reported in an earlier paper (Ingram *et al.*, 1979, Tables 2 and 3).

Results

The association between anisometropia and astigmatism was first noticed among our children who were refracted after atropinisation (Ingram, 1979) (Table 5). For future reference attention is drawn

Table 1 *Refractions of individual eyes*

	Age 1 year	*Age 3½ years*	*Difference*
Incidence of hypermetropia +2·00 or more DS	33/296 = 11·0%	36/296 = 12·2%	Not significant
Incidence of astigmatism +1·50 or more D	35/296 = 11·8%	15/296 = 5·1%	P<0·01
Incidence of astigmatism +1·00 or more D	88/296 = 29·7%	23/296 = 7·8%	P<0·001

Table 2 *Refractions of children*

	Age 1 year	*Age 3½ years*	*Difference*
Incidence of bilateral hypermetropia +2·00 or more DS	16/148 = 10·8%	17/148 = 11·5%	Not significant
Incidence of astigmatism of +1·50 or more D in either or both eyes	23/148 = 15·5%	10/148 = 6·7%	P=2·68%
Incidence of anisometropia	12/148 = 8·1%	13/148 = 8·8%	Not significant

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to a similar association at ages 1 year and 3½ years (Table 3). This association is highly significant at both ages in spite of the fact that 7 children were anisometropic at 1 year but not at age 3½, their places being taken at age 3½ by 8 children who were not anisometropic at age 1 year.

It is also true to say that at both ages an anisometropic eye was significantly more likely to have +1·50 or more D of astigmatism (irrespective of whether the fellow eye is also astigmatic). At age 1 year P<0·001; at age 3½ years P<0·001.

The refractions of these children have been recorded in 4 different ways so that the range of refractions at age 1 year could be compared with those at 3½ years (Table 4): (1) The basic spherical refraction of the more emmetropic of a pair of eyes, thus recording 1 figure for each child, but completely ignoring astigmatism and anisometropia (Fig. 1). (2) The mean of the spherical equivalents of each of a pair of eyes, which makes some allowance for astigmatism and anisometropia when present, but again records 1 single figure for each child. (3) The basic spherical refraction of individual eyes, recording 2 figures for each child, thus making some allowance for anisometropia but none for astigmatism (Fig. 2). (4) The spherical equivalents of individual eyes, again recording 2 figures for each child, but reflecting to some extent both astigmatism and anisometropia. The variances were calculated for all 8 sets of refractions. No significant differences were found when any pair within any of the 4 groups were compared.

The changes in refraction of the horizontal and vertical meridia are summarised in Tables 5 and 6. The difference between each group of both meridia

Table 3 *Anisometropia and astigmatism*

	Not aniso.	*Aniso.*	*Total*
Age 1 year:			
< +1·50 D cyl. in both eyes	124	2	126
+1·50 or more D cyl. in either or both eyes	12	10	22
Total	136	12	148
P=0·000 003%			
Age 3½ years:			
< +1·50 D cyl. in both eyes	131	6	137
+1·50 or more D cyl. in either or both eyes	4	7	11
Total	135	13	148

P=0·000 178%

Table 4 *Range of refractions at age 1 and 3½*

Group	*Age*	*Mean*	*Standard deviation*	*Significance of difference*
(1)	1	+0·61	1·06	5%
	3½	+0·89	1·00	
(2)	1	+0·95	1·09	NS
	3½	+1·10	1·07	
(3)	1	+0·62	1·11	1%
	3½	+0·95	1·11	
(4)	1	+0·97	1·10	NS
	3½	+1·12	1·07	

NS = Not significant

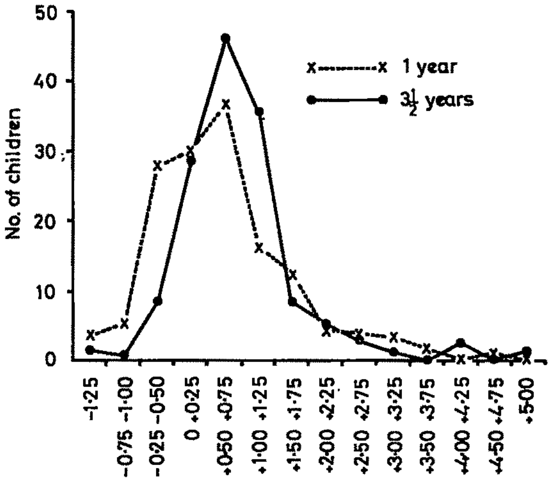

Fig. 1 *Distribution curve: basic spherical refraction of better eye*

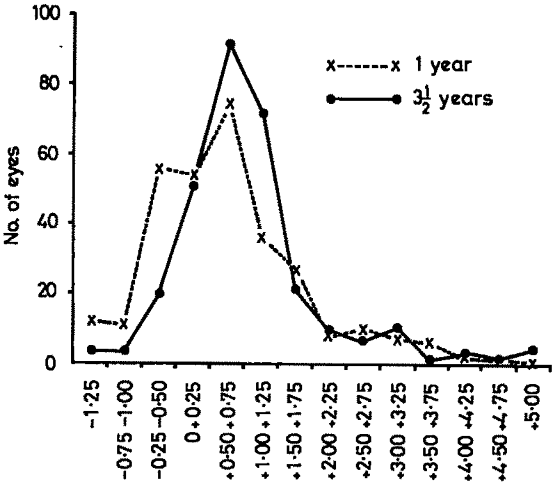

Fig. 2 *Distribution curve: basic spherical refraction of individual eyes*

Table 5 *Changes in refraction of horizontal and vertical meridia of individual eyes*

Initial refraction	*Horizontal meridian* −1·25 *More myopia*	−1·00 −0·75	−0·50 −0·25	0 +0·25	+0·50 +0·75	+1·00 +1·25	+1·50 +1·75	+2·00 +2·25	+2·50 +2·75	+3·00 +3·25	+3·50 +3·75	+4·00 +4·25	+4·50 +4·75	+5·00 *More hyper-metropia*
Change in refraction														
+	6	8	24	32	33	15	4	4	6	3	4	1	2	0
0	0	0	5	11	25	8	6	3	1	3	0	0	0	0
−	2	2	1	3	13	25	24	12	6	5	1	2	0	0
	Vertical meridian													
+	6	3	35	33	38	8	9	7	3	1	4	3	0	2
0	0	0	11	10	22	9	4	4	2	4	0	0	0	0
−	2	2	2	4	10	25	18	9	5	1	2	2	0	0

+ = More hypermetropic or less myopic. 0 = No change. − = Less hypermetropic or more myopic

Table 6

Range of refraction at age 1 year		*Change* *Horizontal meridian* +	 *0*	 −	*Change* *Vertical meridian* +	 *0*	 −
Group 1	Myopia to +0·75 D	103	41	21	115	43	20
Group 2	+1·00 to +2·25 D	23	17	61	24	16	52
Group 3	+2·50 or more D	16	4	14	13	6	10

is statistically significant except for Group 2 versus Group 3 in the vertical meridian.

Discussion

There is no evidence to indicate that the incidence or amount of hypermetropia decreased between the ages of 1 and 3½ years. Of four possible methods used to record the range of refractions of these children the mean moved significantly towards the hypermetropic side in 2 instances. There was no significant difference when either of the other 2 methods were used.

If the concept of emmetropisation was correct, the spread of the curve representing the range of refractions at age 1 year should narrow by the age of 3½ years, but this did not occur.

There is quite clearly a highly significant decrease in the incidence of astigmatism both in individual eyes and in the number of children who have astigmatism of +1·50 or more D in either or both eyes. Possibly there may be a resurgence of interest in astigmatism and its effects on visual acuity, and it seems natural to study the changes that occurred in the refraction of the horizontal and vertical meridia of individual eyes. Astigmatism is not always in the 90° or 180° axis, but for simplicity the refraction of the meridian nearest to the horizontal and vertical axis has been recorded as that of the horizontal and vertical axis respectively. If at the age of 1 year the refraction in either meridian was myopic or less than +2·50 D, there was a definitely significant trend towards emmetropia (+0·50 to +1·25 D). Thus there is unequivocal evidence to support Fabian's (1966) theory of emmetropisation *if this is applied to the refraction of individual meridia between the ages of 1 and 3½ years.*

If the refraction in either meridian at age 1 year was +2·50 or more D, it seems that the change in refraction in that meridian is against the above trend, that is the refraction became either more or less hypermetropic by the age of 3½ years. This is, however, significant only in the case of the horizontal meridian, although the trend appears similar in the vertical meridian.

It has been suggested (Ingram, 1977) that the absence of a refractive error (by implication hypermetropia and/or anisometropia) at the time a child presents with squint and/or amblyopia might not preclude an abnormal refraction earlier in life. It would have been convenient if this analysis had shown an overall decrease in hypermetropia between the ages of 1 and 3½ years, but this does not occur. However, preliminary observations on the changes in refraction between the ages of 6 and 12 months do show a consistent decrease in hypermetropia in only those eyes, or meridia, which are hypermetropic at age 6 months. Thus it may be that between the ages of 1 and 3½ years there is a fine tuning in an overall process of emmetropisation with, in particular, a shift of the mildly myopic refractions towards hypermetropia. It will be necessary to trace the changes in refraction from the first few weeks of life through to 3½ years and later in order to complete the picture.

We thank Mrs Rodgers for doing the calculations for us and Mrs Neale for secretarial help.

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Refraction of 1-year-old children after atropine cycloplegia

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SUMMARY The refractions of 1648 children aged 11 to 13 months are reported. Atropine 1% was used for cycloplegia. 11·83% of the children had bilateral hypermetropia of +2·00 or more D. 13·23% of them had +1·50 or more D astigmatism in one or both eyes, and 6·5% had anisometropia. Anisometropia was significantly (P=0·000 001%) associated with bilateral hypermetropia, but even more significantly (P=0·000 000 4%) associated with astigmatism of +1·50 or more D in one or both eyes.

Cyclopentolate was used in our pilot study (Ingram *et al.*, 1979) for reasons of convenience, but its cycloplegic effect has not been proved (Davidson, 1976). Atropine is accepted generally as the most efficient cycloplegic drug, and the true range of refractions at age 1 year would be more accurately recorded after 'atropinisation'. This is a report of the refractions of 1648 1-year-old children examined after 'full atropinisation'. The findings are compared with those of other 1-year-old children refracted after instillation of cyclopentolate in a subsequent publication (Ingram and Barr, 1979).

Sample of children

The children were all born between 1 January 1974 and 31 December 1976. They were registered at the time of their first birthday under one of the partners in seven adjacent group general medical practices in the Kettering district.

Methods

Mothers were introduced to the idea of vision screening by the health visitors when the child had a hearing test at the age of 9 months. Those wishing to have their children's eyes examined were subsequently issued with written instructions on how to instil 1% atropine ointment twice daily for the 4 days preceding their appointment. The examinations were carried out in the respective general practitioners' premises.

The plan was to screen the children during the month of their birth, but some children born late in the month were refracted early in that month and others, for one reason or another, attended during the following month. Thus their ages ranged from 11 to 13 months inclusive.

All the refractions were carried out by the author. When cycloplegia was obviously incomplete, for example, the pupils were mobile or when the refraction changed during retinoscopy, the refraction was excluded. Anybody experienced in refracting children will, however, recognise that there are occasions when complete cycloplegia is in doubt in spite of the pupils being fixed and the refraction appearing to be static, and such children have been included.

The refractions were recorded as before (Ingram, 1977), the basic spherical refraction being that of the less hypermetropic or more myopic meridian for each eye, with any astigmatism (in + cylinders) or anisometropia being recorded separately.

Children found to have squint or congenital abnormalities were managed on traditional lines.

Results

A variety of clinical and pathological conditions were either identified at the time of screening or previously known (Tables 1 and 2).

A summary of the figures for the basic spherical refraction of individual eyes is given in Table 3. There is no significant difference between any of these 3 samples of children. Distribution curves drawn for each individual sample are so similar that 1 composite curve is presented (Fig. 1).

Figures for the refractions of children recorded as the basic spherical refraction of the more emmetropic eye are summarised in Table 4. There

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Table 1 *Particulars of the sample of children available for screening*

	Born 1974	*Born 1975*	*Born 1976*
Total number available for screening	987	941	896
Number who 'declined' examination	104	139	136
Number who did not attend	285	249	216
Number who attended but were not 'fully atropinised'	17	7	19
Number where refraction was impossible	2	0	2
Number who were refracted	579	546	523

Table 2

	Born 1974	*Born 1975*	*Born 1976*
Esotropia	4	3	3
Esotropia + nystagmus	1	—	—
Exotropia + dislocated lens	1	—	—
Coloboma of uveal tract	—	1	—
Coloboma of uveal tract + esotropia	—	1	1
Congenital cataract	—	1	—
Congenital nystagmus	—	—	2
Buphthalmos	—	—	1
Angioma of eyelid	—	1	—
Heterochromia iridis	1	—	—
Gross anomaly of ocular movements	1	—	—

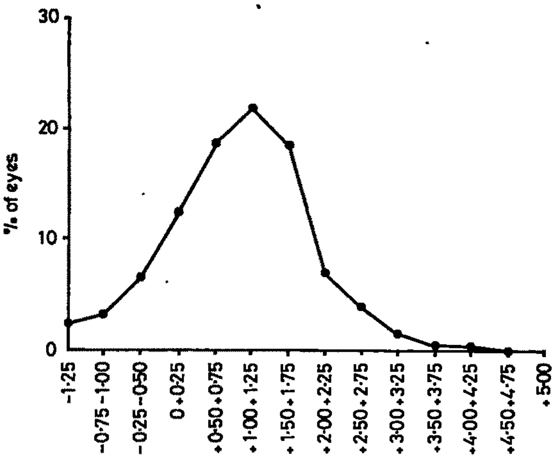

Fig. 1 *Spherical refraction of eyes, age 1 year, atropine,* n = *3296*

Table 3

	Mean	*SD*	*SE*
Born 1974	0·9817	1·0181	0·0299
Born 1975	0·9771	1·0626	0·0322
Born 1976	1·0019	0·9865	0·0305

Table 4

	Mean	*SD*	*SE*
Born 1974	0·9593	0·9533	0·0396
Born 1975	0·9270	0·9779	0·0418
Born 1976	0·9136	0·9234	0·0405

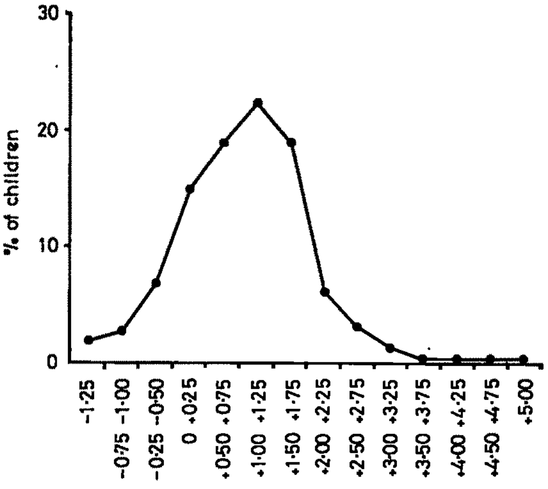

Fig. 2 *Spherical refraction of better eye, age 1 year, atropine,* n = *1648*

is no significant difference between any of these 3 samples of children. Again, the distribution curves drawn for each sample are so similar that 1 composite curve is presented (Fig. 2).

The incidence of astigmatism differs most between children born in 1974 and those born in 1975. However, this difference is not significant in terms of the numbers of individual eyes with +1·50 or more astigmatism (P=6·148%) or of the number of children who had this amount of astigmatism in either or both eyes (P=59·806%) (Table 5). The difference in the incidence of children who had anisometropia is most marked when children born in 1974 are compared with those born in 1976, but it is not significant (P=5·617%).

The overall incidence of anisometropia was 107/1648, that is, 6·5%. The overall incidence of

Table 5 *Incidence of spherical hypermetropia, astigmatism, and anisometropia*

	Born 1974	*Born 1975*	*Born 1976*
Number of children with bilateral spherical hypermetropia of +2·00 or more DS	77	61	57
Incidence of bilateral spherical hypermetropia	13·3%	11·2%	10·9%
Number of individual eyes with +1·50 or more D astigmatism	102	123	113
Incidence of astigmatism +1·50 or more D in individual eyes	8·8%	11·3%	10·8%
Number of children who had +1·50 or more D astigmatism in one or both eyes	66	81	71
Incidence of astigmatism +1·50 or more D in one or both eyes	11·4%	14·8%	13·6%
Number of children who had anisometropia	45	37	25
Incidence of anisometropia	7·77%	6·77%	4·78%
Incidence of bilateral hypermetropia and/or anisometropia	104/579 = 17·96%	90/546 = 16·48%	76/523 = 14·53%
Incidence of bilateral hypermetropia and/or astigmatism of +1·50 or more D in one or both eyes	131/579 = 22·62%	134/546 = 24·54%	119/523 = 23·30%

Table 6 *Association between anisometropia and spherical hypermetropia*

	< +2·00 DS		*+2·00 DS or more*	
	No aniso.	*Aniso.*	*No aniso.*	*Aniso.*
Children born 1974	951	29	162	16
Children born 1975	912	26	143	11
Children born 1976	876	13	145	12
Total	2739	68	450	39

	No aniso.	*Aniso.*	*Total*
< +2·00 DS	2739	68	2807
+2·00 or more DS	450	39	489
Total	3189	107	3296

P=0·000 000 1%

bilateral spherical hypermetropia was 195/1648, that is 11·83%. The overall incidence of bilateral hypermetropia and/or anisometropia was 270/1648, that is, 16·38%. The overall incidence of bilateral hypermetropia and/or astigmatism was 384/1648, that is, 23·30%. 13·23% of the children had +1·50 or more D astigmatism in one or both eyes.

An anisometropic eye is significantly more likely to be hypermetropic, for example, have a basic spherical refraction of +2·00 DS or more and vice versa (Table 6).

Also a child with bilateral spherical hypermetropia is significantly more likely to have an anisometropic eye and vice versa (Table 7).

An anisometropic eye is significantly more likely to have astigmatism of +1·50 or more D and vice versa (Table 8).

Table 7

	< 2·00 DS		*+2·00 or more DS in both eyes*	
	No aniso.	*Aniso.*	*No aniso.*	*Aniso.*
Children born 1974	475	27	59	18
Children born 1975	456	29	53	8
Children born 1976	447	19	51	6
Total	1378	75	163	32

	No aniso.	*Aniso.*	*Total*
< +2·00 DS	1378	75	1453
+2·00 or more DS	163	32	195
Total	1541	107	1648

P=0·000 001%

Table 8 *Association between anisometropia and astigmatism*

	< +1·50 D cyl.		*+1·50 D cyl. or more*	
	No aniso.	*Aniso.*	*No aniso.*	*Aniso.*
Children born 1974	1039	17	74	28
Children born 1975	955	14	100	23
Children born 1976	923	10	98	15
Total	2917	41	272	66

	No aniso.	*Aniso.*	*Total*
< +1·50 D cyl.	2917	41	2958
+1·50 or more D cyl.	272	66	338
Total	3189	107	3296

P=0·000 000 012%

Also, a child with +1·50 D or more astigmatism in either or both eyes is significantly more likely to have an anisometropic eye and vice versa (Table 9).

Discussion

57 to 59% of the available children were refracted in each year, but those examined were not necessarily representative of the whole. Information relevant to this point, such as social class, was unfortunately not obtained.

There is no significant difference in the findings of the children born in each of the years 1974, 1975, and 1976 (Tables 1–4). The apparent decrease in the number of anisometropes has possibly arisen because the author became more conscious of the significance of anisometropia, and this might have influenced interpretation of when the retinoscopy shadows actually 'turned'. It is also a timely reminder of how arbitrarily the criteria for 'anisometropia' were selected and that in reality isometropia gradually merges into anisometropia. For example, a child who has 2 eyes with a refraction differing by +0·75 DS/+0·75 D cyl. could be more 'anisometropic' than one whose eyes differed by just +1·00 DS or +1·00 D cyl.

When the refractions of those children born in 1974 were summarised, it was noted that the incidence of children having hypermetropia and/or anisometropia was 17·9%.6 This was close to the figure of 20% that had been suggested (Ingram, 1977) might be found in the child population as a whole. Attention then became focused on the incidence of anisometropia alone. Mindful of Ikeda and Wright's (1975) hypothesis that infantile anisometropia might cause stimulus deprivation amblyopia, the finding that 7·77% of 1-year-old children born in 1974 had anisometropia seemed particularly interesting, because approximately 7% of children present at some time with squint and/or amblyopia. There was also a highly significant association in this one year's sample between anisometropia and bilateral spherical hypermetropia (Table 10).

However, there was an even more significant association between anisometropia (of +1·00 or more D sphere and/or +1·00 or more D cyl.) and the presence of +1·50 or more D astigmatism in either or both eyes of a child (Table 11). This association was confirmed in the samples of children born in 1975 and 1976 and also in the overall figures for the 3 years added together: anisometropia and hypermetropia (Table 7, P=0·000 001%); anisometropia and astigmatism (Table 9, P=0·000 000 4%). This may be a very significant finding and it poses the question whether, if meridional amblyopia is a form of stimulus deprivation amblyopia (Mitchell *et al.*, 1973, Noorden, 1974), 'anisometropic' amblyopia as we understand the term might also be due to stimulus deprivation. It also led us to consider what might be the effects of an abnormal amount of hypermetropia in one or more meridia on the development of vision during the sensitive period (see Ingram *et al.*, 1979).

Table 9

	< +1·50 D cyl. in both eyes		*+1·50 D cyl. in either eye*	
	No aniso.	*Aniso.*	*No aniso.*	*Aniso.*
Children born 1974	496	17	38	28
Children born 1975	452	13	57	24
Children born 1976	442	10	56	15
Total	1390	40	151	67

	No aniso.	*Aniso.*	*Total*
< +1·50 D cyl. in both eyes	1390	40	1430
+1·50 or more D cyl. in either eye	151	67	218
Total	1541	107	1648

P=0·000 000 4%

Table 10

	No aniso.	*Aniso.*	*Total*
< +2·00 DS	475	27	502
+2·00 or more DS	59	18	77
Total	534	45	579

P<0·0001%

Table 11

	No aniso.	*Aniso.*	*Total*
< +1·50 D cyl.	496	17	513
+1·50 or more D cyl.	38	28	66
Total	534	45	579

P<0·0001%

I thank the following general medical practitioners and their partners for permission to use their premises and staff and to examine their patients: Drs Deutsch, Emanuel, Harlow, Lawson-Matthew, Padget, Shemilt, and Walker. It would have been impossible to do this work without the wholehearted support of their respective health visitors, and I thank them all for the many hours they have spent explaining the reasons for the screening to the mothers and organising the appointments.

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British Journal of Ophthalmology, 1979, **63**, 348–352

Refraction of 1-year-old children after cycloplegia with 1% cyclopentolate: comparison with findings after atropinisation

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SUMMARY Cyclopentolate 1% is significantly less effective than atropine 1% at producing cycloplegia in 1-year-old children. If cycloplegic refraction is to be used for investigation or screening children for visual defects *during the sensitive period*, the more prolonged and profound cycloplegia following atropine could potentially have a disastrous effect on the development of vision. Cyclopentolate 1% would have to be used, and allowance made for its inadequacy as a cycloplegic.

The feasibility study of screening 1-year-old children (Ingram *et al.*, 1979) was followed up and extended into adjacent parts of this district using atropine 1% and cyclopentolate 1% for cycloplegia. If retinoscopy after cycloplegia is to be used for further investigation of the possibility of preventing amblyopia and squint, and if it is ever to become a recognised method of screening large numbers of infants for visual defects, the choice of cycloplegic drug might be important. The advantages and disadvantages of atropine and cyclopentolate, the 2 drugs that are probably most commonly used, need to be compared, particularly with regard to (1) their efficiency as a cycloplegic; (2) their side effects and safety; (3) whether the mothers had a preference for one or the other, because it is no good having an efficient screening test if the public cannot be persuaded to use it.

Samples of children

Children born between January 1975 and December 1976 and registered on their first birthday with 3 group practices in the town of Rushden were used in this investigation. Those born in 1975 had cyclopentolate 1% instilled once, 30 minutes before retinoscopy. Those born in 1976 had cyclopentolate 1% instilled twice, 40 and 30 minutes before retinoscopy. The mothers instilled the cyclopentolate drops, as it was thought it would be more convenient for them and the clinical staff.

The findings have been compared with those refracted after atropine cycloplegia (Ingram, 1979) and with the sample of children reported in the pilot study (Ingram *et al.*, 1979).

Methods

The organisation of the screening was the same as that described for the children refracted after atropine cycloplegia (Ingram, 1979). All the refractions were performed by the same person (R. M. I.).

The refractions of the various groups were then compared to see if (1) The basic spherical refractions of one group were more hypermetropic than another. That is, was the mean spherical refraction different when one group was compared with another? (2) The range of the basic spherical refractions of individual eyes or children was different in one group to that of another. That is, did the spread of the curve differ between individual groups? (3) The incidence of astigmatism and/or anisometropia differed.

Results

There is no significant difference between the mean or the spread of the distribution curves for any of these 3 samples of children when either the basic spherical refraction of individual eyes (Table 2) or the basic spherical refraction of the more emmetropic eye was recorded (Table 3).

There is no significant difference in the incidence of any of these refractions between children born in 1975 and 1976 (Table 4).

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Table 1 *Particulars of the samples of children screened after cyclopentolate 1%*

	Born 1975	*Born 1976*
Total number available for screening	355	415
Number who 'declined' examination	4	3
Did not attend	52	83
Refraction impossible	6	6
Others—squint, congenital abnormalities, etc.	2	0
Number who were refracted	291 (82%)	323 (78%)

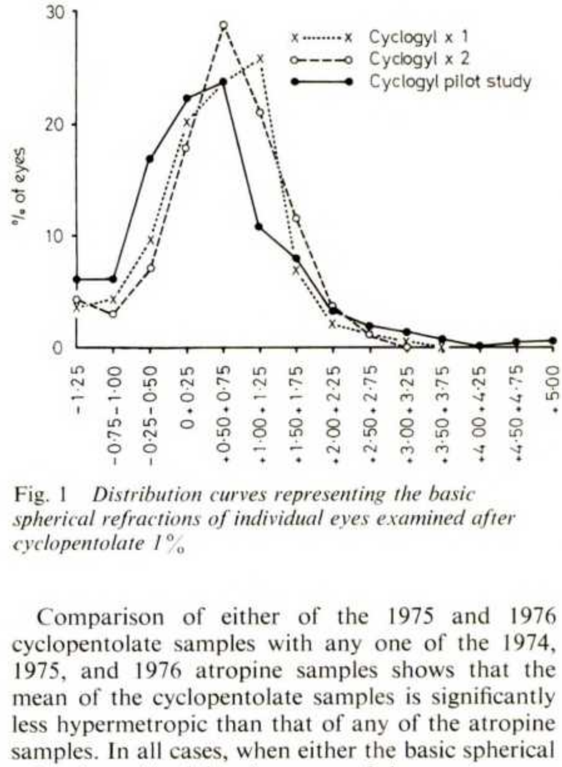

Fig. 1 *Distribution curves representing the basic spherical refractions of individual eyes examined after cyclopentolate 1%*

Comparison of either of the 1975 and 1976 cyclopentolate samples with any one of the 1974, 1975, and 1976 atropine samples shows that the mean of the cyclopentolate samples is significantly less hypermetropic than that of any of the atropine samples. In all cases, when either the basic spherical refraction of individual eyes or of the more emmetropic eye of a child is recorded, the difference is significant at the 1% level.

Moreover, the incidence of bilateral spherical hypermetropia of +2·00 or more D is significantly higher after cycloplegia with atropine than it is after the use of cyclopentolate (Table 5).

The means of the cyclopentolate 1975 and 1976 samples are significantly different for the horizontal meridian at the 5% level but not for the vertical meridian. The spreads of the distribution curves for these samples are not significantly different in either meridian. In both the cyclopentolate samples the means of the horizontal meridian are significantly different from the means of the vertical meridian at the 1% level. There is no such difference in the atropine samples. It is not known whether this is due to the cycloplegic drug or to different population samples. There is no significant difference between the means or the spreads of the distribution curves of any of the atropine 1974, 1975, and 1976 samples in either meridian. The means of both the cyclopentolate samples differ significantly at 1% level from the means of each of the atropine samples in both meridia. The spreads of the distribution curves of both cyclopentolate samples differ significantly, at the 5% level or less, from the spreads of the distribution curves of all the atropine samples in both meridia.

Table 2 *Basic spherical refractions of individual eyes and children*

	Mean	*SD*	*SE*
Born 1975	0·59	0·88	0·04
Born 1976	0·58	1·05	0·05
Pilot study	0·64	0·82	0·03

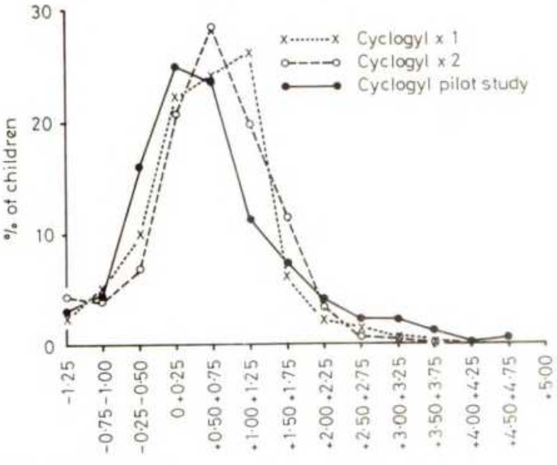

Fig. 2 *Distribution curve representing the basic spherical refractions of the more emmetropic eye of children examined after cyclopentolate 1%*

Table 3

	Mean	*SD*	*SE*
Born 1975	0·55	0·81	0·05
Born 1976	0·59	0·80	0·04
Pilot study	0·55	1·00	0·07

Table 4 *Incidence of spherical hypermetropia, astigmatism, and anisometropia after refraction following cyclopentolate 1%*

	Born 1975	*Born 1976*
Number of children with bilateral spherical hypermetropia of +2·00 or more DS	11	14
Incidence of bilateral spherical hypermetropia	3·78%	4·33%
Number of individual eyes with +1·50 or more D astigmatism	75	93
Incidence of astigmatism +1·50 or more D in individual eyes	12·88%	14·40%
Number of children who had +1·50 or more D astigmatism in either or both eyes	47	60
Incidence of astigmatism of +1·50 or more D in either or both eyes	16·15%	18·57%
Number of children who had anisometropia	17	17
Incidence of anisometropia	5·84%	5·26%
Incidence of bilateral hypermetropia and/or anisometropia	27/291 = 9·28%	30/323 = 9·28%
Incidence of bilateral hypermetropia and/or astigmatism	57/291 = 19·59%	71/323 = 21·99%

Table 5 *Comparison of the basic spherical refractions after cyclopentolate and atropine cycloplegia*

	1974–76 Atropine	*1975–76 Cyclopentolate*	*Total*
< +2·00 DS in both eyes	1453	589	2042
+2·00 or more DS in both eyes	195	25	220
Total	1648	614	2262

P<0·001

There was a lower incidence of anisometropia detected after cyclopentolate than after atropine, but this difference was not significant. However, an anisometropic eye more often than not has +1·50 or more D astigmatism, and if the ratio of anisometropic eyes with and without this astigmatism is examined there is a marked difference between the 1976 cyclopentolate sample and the others, which cannot be explained.

There was a higher incidence of astigmatism in the samples refracted after cyclopentolate, which is significantly different when the 1976 sample is compared with the sum of the atropine samples.

Discussion

While this is not an ideal method of comparing 2 drugs, there was no other practical alternative. Moreover, there was no means of knowing whether either cycloplegic was instilled strictly according to instructions. A mobile pupil obviously suggests incomplete cycloplegia, but a fixed mydriasis is not necessarily an indication of the amount of cycloplegia. Cyclopentolate seems to give variable mydriasis in young children, and this has been reported especially in premature infants (Carpel and Kalina, 1973). On occasions repeated instillations of cyclopentolate by one of us personally (R. M. I.) has failed to increase mydriasis, and even atropine does not invariably produce full mydriasis, particularly in coloured races.

CYCLOPLEGIA AFTER CYCLOPENTOLATE AND ATROPINE

Observations on the children refracted after cyclo-

Table 6 *Refractions in the horizontal and vertical meridia of individual eyes*

Sample	*Horizontal meridian*		*Vertical meridian*	
	Mean	*SD*	*Mean*	*SD*
Atropine 1974	+1·21	1·07	+1·16	1·07
Atropine 1975	+1·27	1·11	+1·19	1·11
Atropine 1976	+1·28	1·02	+1·23	1·07
Cyclopentolate 1975	+0·96	0·90	+0·78	0·91
Cyclopentolate 1976	+1·06	0·91	+0·82	0·94

Table 7 *Anisometropia and astigmatism*

	Atropine			*Cyclopentolate*	
	1974	*1975*	*1976*	*1975*	*1976*
<1·50 D astigmatism	17	14	10	6	1
1·50 or more D astigmatism	28	23	15	11	16
Ratio	1·65:1	1·64:1	1·50:1	1·83:1	16:1

Table 8 *Comparison of the incidence of astigmatism +1·50 D or more*

	Level of significance, %
1975 Cyclopentolate versus 1974–76 atropine:	
incidence in individual eyes	6·81
incidence in either or both eyes of a child	8·46
1976 Cyclopentolate versus 1974–76 atropine:	
incidence in individual eyes	0·26
incidence in either or both eyes of a child	1·48

pentolate cycloplegia show a lower amount of hypermetropia than is the case after atropinisation. This could have been in some way connected with the apparently higher incidence of astigmatism found after cyclopentolate cycloplegia, so the refractions found in the horizontal and vertical meridia were compared, but again there was a significantly (at 1% level) lower amount of hypermetropia in both meridia when cyclopentolate was used. The consistently lower amount of hypermetropia recorded after the use of cyclopentolate than after atropine (approximately 0·40 D) is well illustrated by the significantly lower incidence of bilateral hypermetropia, and it is clear that the cycloplegic effect of 1% cyclopentolate is not as profound as that of atropine 1%. On the other hand it does not seem to matter whether mothers or nurses instilled the cyclopentolate, or whether the drops were instilled once or twice (Figs. 1 and 2).

In the past cyclopentolate has been compared (for mydriasis and cycloplegia) with homatropine (various percentages) plus or minus ephedrine (Abraham, 1953; Stolzar, 1953; Milder and Riffenburgh, 1953; Ehrlich, 1953; Gettes, 1954; Gordon and Ehrenburg, 1954; Mitchell *et al.*, 1958) but so far as we are aware only once with atropine. Cowan and Archer (1962), reporting on 20 'representative cases', found that if the pupils were not actively mobile cyclopentolate was as effective a cycloplegic as atropine. However, their cases were all children attending for squint and amblyopia and were not necessarily representative of the whole.

It is not known why there was a higher incidence of astigmatism found in the children refracted after cyclopentolate. This has been considered from various angles, and, although it is possible that cyclopentolate in some way 'reveals' more astigmatism, it is quite likely that the incidence of astigmatism (or other abnormal refractions) may vary in different population samples.

SAFETY

If it were to be established that hypermetropia in one or more meridia (over and above the ability of that eye to accommodate) during the sensitive period was the basic cause of amblyopia and squint, it is obvious that prolonged cycloplegia (as after the use of atropine) during this period would very likely potentiate stimulus deprivation and itself contribute towards amblyopia. Indeed, this is exactly what the recent experiments of Ikeda and Tremain (1978) suggest will happen. In our experience atropine used at the age of 1 year has not led to amblyopia, *but in the first 3 months of life atropine may well be absolutely contraindicated.*

It is proposed to continue investigations in children at the age of 6 months (and in even younger children at a later date) using cyclopentolate 1% in spite of doubts about its efficacy as a cycloplegic. The answer to the problem of identifying those children who would present with squint and amblyopia untreated is unlikely to be pure black-and-white with a clear-cut dividing line. Ultimately the important point will be whether a child who has a refraction of more than a given number of dioptres will have a significant chance of being cured by preventive treatment. The number of dioptres would be relevant to a particular, named, cycloplegic drug, and might be a lower figure if cyclopentolate were used rather than if atropine.

SIDE EFFECTS OF CYCLOPENTOLATE AND ATROPINE

Photophobia resulting from the prolonged mydriasis after atropine was the side effect most commonly remarked on by parents. This worries them because many think that bright light is bad for the eyes, particularly during the summer months, when it might deter them from having their children's eyes screened. This photophobia did not cause concern after cyclopentolate. The absence of prolonged photophobia and the convenience of 2, as opposed to 8, instillations of cycloplegic probably accounted for the higher attendance rate for screening after cyclopentolate. There were no allergic reactions to either drug.

No signs of systemic side effects were found after either drug was used in these children. However, there are isolated reports of systemic toxicity after using Cyclogyl 1% (Simcoe, 1962; Bauer *et al.*, 1973) and after using Cyclogyl 2% (Beswick, 1962; Binkhurst *et al.*, 1963; Praeger and Miller, 1964). All these psychotic reactions were what one would anticipate in view of the parasympatholytic action of the drug, and with the exception of those in a child reported by Bauer *et al.* (1973) all were transient, lasting only a few hours.

We thank Drs Clarke, Lumb, and Smith and their partners for permission to screen their patients with cyclopentolate. We thank Mrs Griffin and Mrs Hughes, the health visitors who have provided the liaison between us and the mothers and who supervised the screening clinics. We also thank Mrs Rodgers for the statistical calculations and Mrs Maddams and Mrs Neale for secretarial help.

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A simple method of detecting abnormal retinal correspondence

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SUMMARY A method is described of determining the state of retinal correspondence by means of an ordinary streak retinoscope used to produce a modified after-image test.

The demonstration of the state of retinal correspondence in a squinting child is a procedure usually left to the orthoptic department in eye clinics in Great Britain. Many different techniques of detecting abnormal retinal correspondence have been developed, the majority requiring complicated and expensive equipment. Probably the most commonly used method is that with the major amblyoscope or one of the variations of the after-image test. One of the latest methods is fixation fundus photography developed by Lang and Wurth (1970), in which they photographed the shadow of a fixation target on the retinae of both eyes. There must be few orthoptic departments with such sophisticated equipment, and, as some ophthalmologists have to work without the benefit of even a simple orthoptic clinic, there exists a need for a quick and easy method of detecting abnormal retinal correspondence without recourse to expensive apparatus or skilled technicians.

Recently I have been trying a very simple technique requiring only the use of an instrument that is readily available in virtually every eye clinic and ophthalmologist's consulting room and which, in this instance, requires very little skill on the part of the user. The instrument is the streak retinoscope, and the method is an adaptation of the after-image test first described by Hering so long ago as 1868 (Hering, 1868).

Methods

The after-image test apparatus, as modified first by Tschermak (1899) and later by Bielschowsky (1938), consisted of a linear light filament inside a glass tube which was fitted with a central metal band around which the tube could be revolved. With the light filament in the vertical position the patient would fixate the central band with 1 eye for about 10 seconds, the other eye being covered. The filament would then be swivelled into a horizontal position and be fixed by the second eye, the first now being covered. This process would imprint an after-image across the maculae of both eyes. After exposure of each eye the filament is switched off and the patient's attention is directed to these images. In a bright room the patient can see dark negative after-images by looking at a plain wall; or in a darkened room, or by closing his eyes, he can see orange-red positive after-images.

Results

If retinal correspondence is normal the after-images form a perfect cross (Fig. 1*a*) irrespective of the position of the eyes relative to each other. In cases of abnormal retinal correspondence the crosses will appear eccentric, or even with their limbs completely separated (Figs. 1*b*, *c*, *d*).

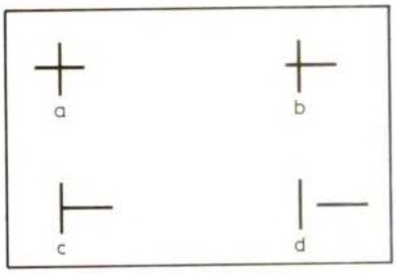

Fig. 1 *Varieties of after-image*

My method of producing the after-images is by using the ordinary streak retinoscope held very close to the patient's eye and asking him to gaze steadily at the light filament. It is important to hold the instrument very still and so it is helpful if its

Address for reprints: Dr Alan Porter, Scarborough Hospital, Scalby Road, Scarborough, North Yorkshire upper end can be rested against the patient's brow. The right eye is exposed to the vertical filament and then the left eye to the horizontal filament, each for a count of 10. It is useful to have a few of the possible combinations of the images drawn on a piece of paper and to ask the patient to point to the one most closely resembling the after-images he sees.

Discussion

The method is successful even in young children and certainly reliable in those capable of co-operating in the Sheridan-Gardner visual acuity test. Any after-image that is not a perfect cross demonstrates the presence of abnormal retinal correspondence.

This method does not, of course, purport to replace a more thorough orthoptic examination, but it does give the busy ophthalmologist a quick and easy way of detecting abnormal retinal correspondence at the time of first examination and with the equipment he already has immediately to hand.

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Silicone oil in the treatment of massive preretinal retraction. I. Results in 105 eyes

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SUMMARY A study of 105 eyes in which intraocular injection of silicone oil was used to treat retinal detachment with massive preretinal retraction showed that early results were encouraging, and anatomical and visual results correlated well. Operative complications had little influence on the immediate outcome, the reasons for failure being poor case selection or inadequate surgical technique. When a deterioration occurred during the postoperative period it was found to be associated with late complications, particularly cataract; redetachment occurred in only a small number (12%) of cases.

'And fill'd their lamps with everlasting oil to give due light...'
(Milton, 1634)

The value of intraocular silicone oil injection in the treatment of complicated retinal detachments has been reported by several authors (Cibis *et al.*, 1962; Cibis, 1964, 1965; Watzke, 1967; Okun, 1968; Scott, 1972, 1973). However, a high incidence of late complications (Watzke, 1967; Okun, 1968) together with poor visual results (Kanski and Daniel, 1973) and reports of silicone oil toxicity (Cockerham *et al.*, 1969; Mukai *et al.*, 1972) have caused this technique to be abandoned in all but a few centres. Disappointing results of conventional methods and also of vitrectomy and the encouraging outcome of silicone oil injection in the management of retinal detachments associated with massive preretinal retraction prompted a careful assessment of this technique in our hands (Grey and Leaver, 1977). Because good initial results were not always maintained, further assessment of a larger series with longer follow-up was necessary.

Patients and methods

Of approximately 1500 cases undergoing retinal detachment surgery in the retinal unit at Moorfields Hospital between October 1973 and March 1978, 105 eyes in 104 consecutive patients in whom the authors used silicone oil injection for the treatment of retinal detachment with massive preretinal retraction were reviewed. A diagnosis of massive preretinal retraction was made when in our combined opinion retinal shortening and rigidity made retinal reattachment by conventional means impossible.

Ninety-seven eyes (92%) had previously undergone conventional treatment for retinal detachment, and 49 (47%) had had more than one previous operation. In 69 eyes (66%) an encircling buckle was already present, in 15 eyes (14%) encirclement was undertaken at the time of silicone oil injection, but in 21 (20%) encirclement was not undertaken.

The surgical technique used was that described by Cibis (1964) and modified by Okun (1968), and Scott (1972). A mean volume of 4·5 ml of silicone oil (1000 cSt viscosity) was injected into the retrohyaloid space via the pars plana by either a screw-down or a three-ring syringe and visualised with the binocular indirect ophthalmoscope.

Assessment of visual acuity was recorded within 1 month and at yearly intervals after surgery, the Snellen chart being used where possible, but otherwise in terms of the patients' ability to count fingers, appreciate hand movements, or perceive light at 1 m. The anatomical status of the retina was assessed by the binocular indirect ophthalmoscope. A case was judged to be anatomically successful if more than half the retina (including the posterior pole) was in apposition to the underlying pigment epithelium. The visual fields were assessed with the Goldmann perimeter before and after surgery in some cases.

Results

ANATOMICAL

Early (105 eyes). Anatomical success was recorded

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in 67 eyes within 1 month of surgery; in 38 eyes the retina was not reattached (Table 1).

Late (93 eyes). Ninety-three eyes were documented at 1 year or longer after surgery. In 51 the retina remained attached throughout the follow-up period, while in 6 late redetachment occurred (Table 2).

VISUAL

Early (105 eyes). Within 1 month of surgery an improvement in vision was recorded in 38 out of 68 phakic eyes, there was no change in 19, and a deterioration had occurred in 11. Of 37 aphakic eyes 20 were improved, 16 were unchanged, and 1 was worse (Table 3, Fig. 1). Of the 67 eyes in which a successful anatomical result was obtained 44 (69%) showed a visual improvement (Fig. 2).

At 1 year (93 eyes). Of 61 phakic eyes assessed 1 year after surgery 22 showed an improvement over the preoperative level, 23 were unchanged, and 16 showed deterioration in vision, while in 32 aphakic eyes 15 were improved, 10 were unchanged, and 7 had deteriorated (Table 4).

Table 1 *Early anatomical results*

	Phakic (68 eyes)	*Aphakic (37 eyes)*	*Total (105 eyes)*
Success	45 (66%)	22 (60%)	67 (64%)
Failure	23 (34%)	15 (40%)	38 (36%)

Table 2 *Late anatomical results*

	Phakic (61 eyes)	*Aphakic (32 eyes)*	*Total (93 eyes)*
Success	34 (56%)	17 (53%)	51 (55%)
Failure	27 (44%)	15 (47%)	42 (45%)

Table 3 *Early visual results*

	Phakic (68 eyes)	*Aphakic (37 eyes)*	*Total (105 eyes)*
Better	38 (56%)	20 (54%)	58 (55%)
Same	19 (28%)	16 (43%)	35 (33%)
Worse	11 (16%)	1 (3%)	12 (12%)

Table 4 *Visual results at 1 year*

	Phakic (61 eyes)	*Aphakic (32 eyes)*	*Total (93 eyes)*
Better	22 (36%)	15 (47%)	37 (40%)
Same	23 (38%)	10 (31%)	33 (36%)
Worse	16 (26%)	7 (22%)	23 (24%)

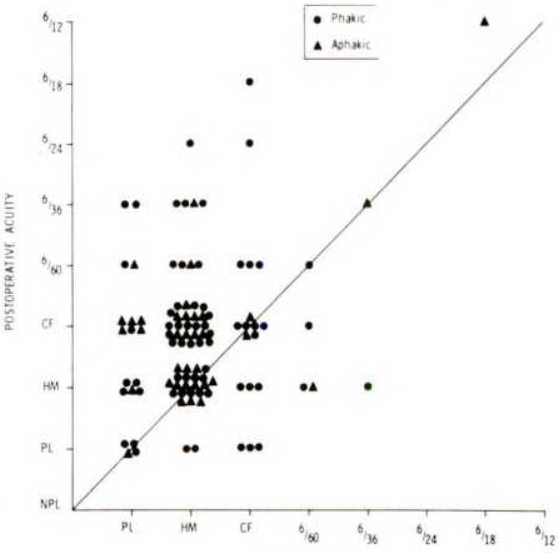

Fig. 1 *Scattergram comparing the preoperative to the early postoperative acuity in 105 eyes. Points on the line show no change, those above improvement, and those below deterioration. NLP = No perception of light. PL = Light perception. HM = Perception of hand movements at 1 m. CF = Finger counting at 1 m*

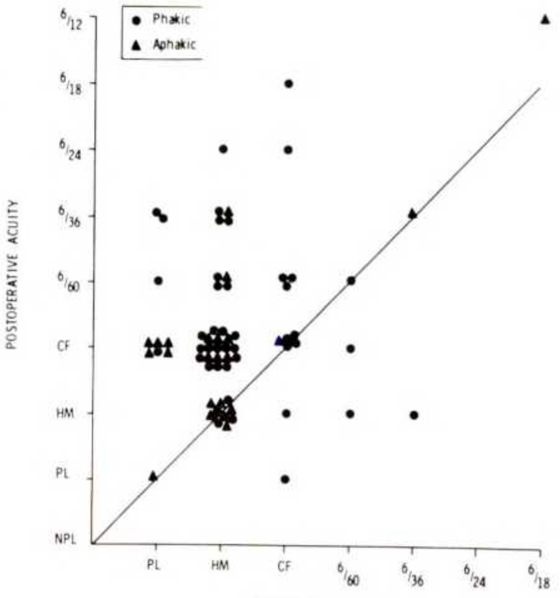

Fig. 2 *Scattergram comparing the preoperaive to the early postoperative acuity in 67 eyes in which reattachment of the retina was achieved*

At 2 years (52 eyes). In 35 phakic eyes assessed at an interval of 2 years after surgery improvement in vision over the preoperative level was maintained in 9, there was no change in 15, and a deterioration was noted in 11, while in 17 aphakic eyes improvement had been maintained in 10, there was no change in 5, and a deterioration had occurred in 2 (Table 5).

At 3 years or longer (29 eyes). Of 20 phakic eyes in which follow-up data were available 3 or more years after surgery 6 showed an improvement over the preoperative vision, 10 were unchanged, and 4 showed a deterioration, while in 9 aphakic eyes 2 were improved, 5 were unchanged, and 2 had deteriorated (Table 6). A separate assessment of those eyes for which follow-up information was available 4 years or more after surgery was not undertaken because of the small number (6 eyes).

Table 5 *Visual results at 2 years*

	Phakic (35 eyes)	*Aphakic (17 eyes)*	*Total (52 eyes)*
Better	9 (26%)	10 (59%)	19 (37%)
Same	15 (43%)	5 (29%)	20 (38%)
Worse	11 (31%)	2 (12%)	13 (25%)

Table 6 *Visual results at 3 years or longer*

	Phakic (20 eyes)	*Aphakic (9 eyes)*	*Total (29 eyes)*
Better	6 (30%)	2 (22%)	8 (28%)
Same	10 (50%)	5 (56%)	15 (52%)
Worse	4 (20%)	2 (22%)	6 (20%)

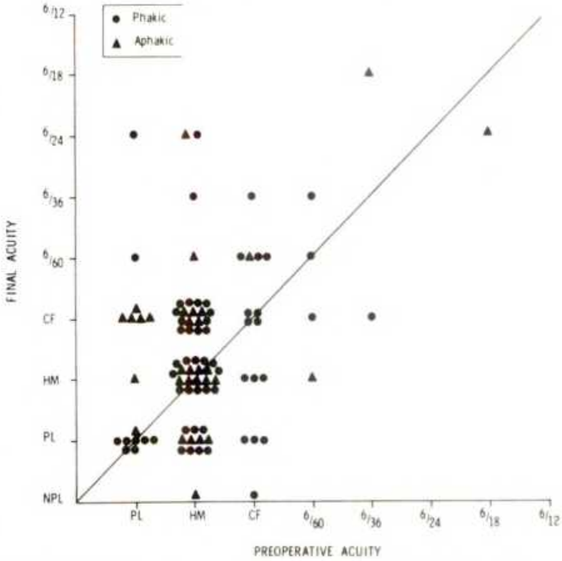

Fig. 3 *Scattergram comparing the preoperative to the final acuity in 93 eyes assessed after 1 year or longer*

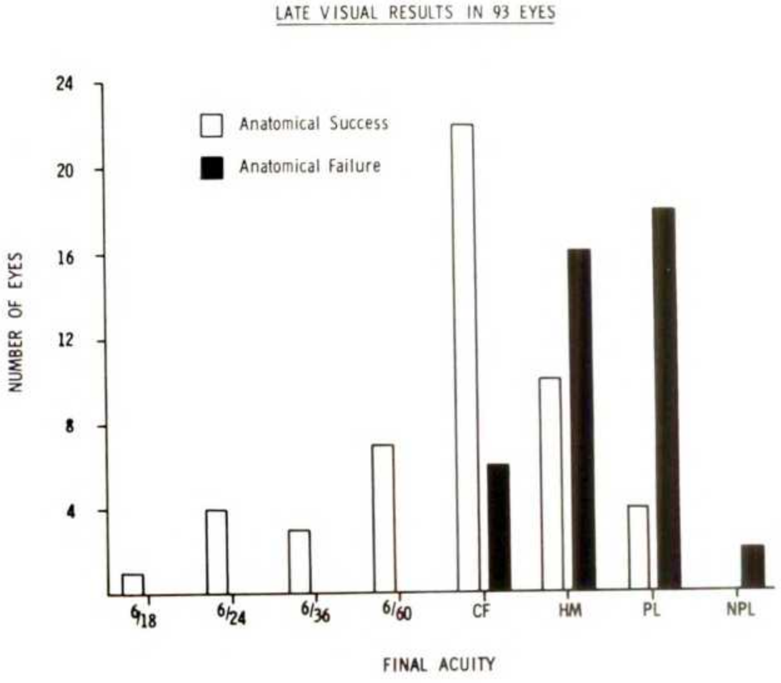

Fig. 4 *Histogram showing the level of acuity in 93 eyes after 1 year or longer*

Comparison of the preoperative acuity with the acuity obtained at the last follow-up visit is illustrated in Fig. 3.

Visual results in anatomically successful cases. Thirty-seven of the 51 anatomically successful cases (73%) maintained navigational vision after 1 year or longer compared with 6 out of 42 patients (14%) in whom the retina was not reattached (Fig. 4). Of the 51 eyes in which the retina remained reattached throughout the follow-up period the initial result

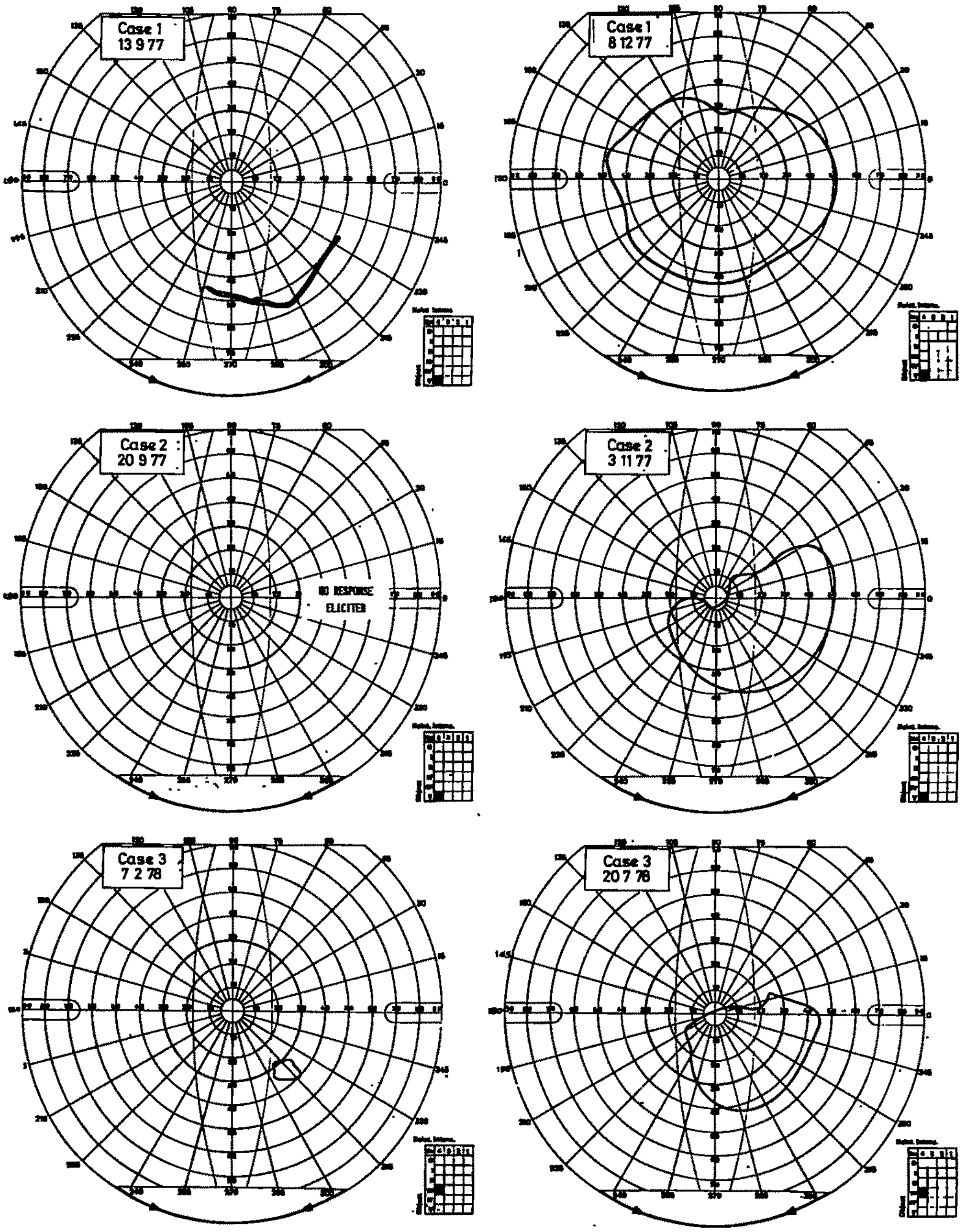

Fig. 5 *Visual fields of 3 patients before and after successful reattachment of the retina. Case 3 had advanced cupping of the optic disc from chronic simple glaucoma*

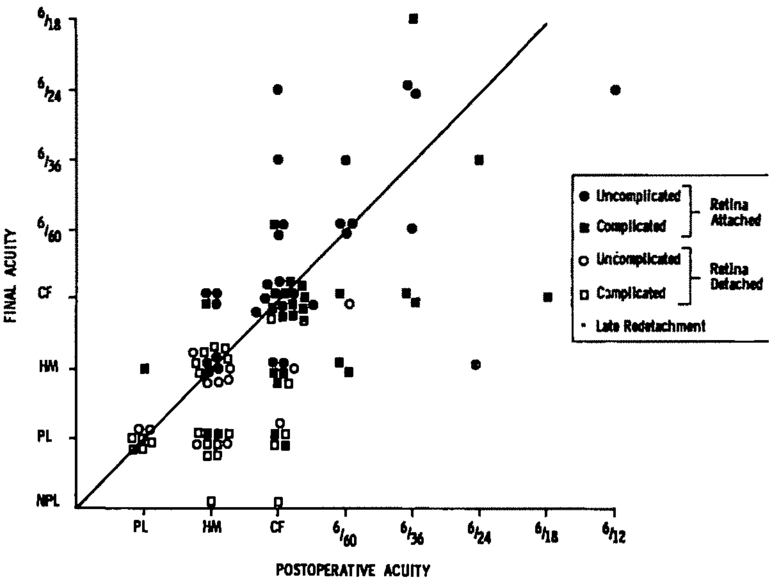

Fig. 6 *Scattergram comparing the early postoperative to the final visual acuity in 93 eyes assessed after 1 year or longer. Points above the line show an improvement during the postoperative period, points on the line no change in the postoperative vision, and points below a deterioration*

was either maintained or improved in 34 (67%).

Visual fields. In all cases in which Goldmann perimetry was done after successful reattachment of the retina a marked improvement in the peripheral field was recorded (Fig. 5).

SURGICAL COMPLICATIONS

Four types of complications occurring at the time of surgery were identified: in 7 eyes silicone oil passed under the retina through a retinal break; in 11 a retinal tear was caused by the injecting needle; in 13 there was haemorrhage from retinal or choroidal blood vessels; and in 2 (both aphakic) silicone oil came forwards into the anterior chamber.

Discussion

The early results of silicone oil injection in the treatment of otherwise irreversible retinal detachments were encouraging both with regard to successful reapposition of the retina and to improvement in visual function (Tables 1 and 3). Furthermore, anatomical and visual results compared well, while the small discrepancy between them might be a reflection of irreversible retinal damage due to longstanding retinal detachment (Cleary and Leaver, 1978). Improvement in vision to a level sufficient for navigation was found to correlate well with successful reapposition of the retina with respect not only to visual acuity (Fig. 4) but also to restoration of peripheral field (Fig. 5).

Complications occurring at the time of surgery had some influence on the operative result. When oil entered the subretinal space it always did so through large retinal tears present before surgery and held open by retinal fibrosis. Small retinal tears caused by the injecting needle did not prevent retinal flattening, and retinal and choroidal haemorrhages were easily controlled by raising the intraocular pressure. When oil entered the anterior chamber at surgery, in aphakic eyes, it did so as a small globule ejected from the needle tip as it passed from the pars plana sclerotomy into the anterior hyaloid. In both cases the oil globule returned behind the pupil after operation and caused no late complication, in contrast to those cases in which forward migration of oil occurred during the postoperative period (Leaver *et al.*, 1979).

Two reasons for deterioration of vision from the early postoperative level could be identified: persistent or recurrent retinal detachment, and development of late complications (Fig. 6). Failure to reattach the retina was due in most cases to poor case selection or inadequate surgical technique. In some cases it was impossible to predict that retinal shortening was irreversible, while in others we failed to evacuate all of the retrohyaloid and subretinal fluid. In a few cases silicone oil passed under the retina through a retinal tear at surgery (Table 7), and in a few instances late redetachment occurred in association with progressive retinal shortening (Fig. 6).

Whereas continuing visual deterioration is understandable when the retina remains detached, in anatomically successful cases it requires explanation. In one-third of the eyes in which the retina remained

Table 7 *Operative complications (26 eyes)*

Haemorrhage	13
Subretinal oil	7
Retinal tear	11
Oil in anterior chamber	2

reattached throughout the follow-up period the vision deteriorated between the early and late assessments, usually in association with late complications (Fig. 6), in particular, cataract (Leaver *et al.*, 1979). Indeed, a striking difference between the visual results in phakic and aphakic eyes is seen at 1 and 2 years after surgery (Tables 4 and 5) owing to the absence of this complication.

The encouragingly high incidence of successful retinal reattachment and the maintenance of visual improvement in the majority of eyes in which anatomical success was achieved confirms that silicone oil injection is an acceptable method of treating otherwise irreversible retinal detachments complicated by massive preretinal retraction. Careful assessment of results indicates that deterioration of vision due to late complications is neither as severe nor as common as previously reported, and in our opinion this method of treatment is certainly justified when the fellow eye is impaired or at risk.

We are grateful to Mr Lorimer Fison and the consultant surgeons at Moorfields Hospital who kindly allowed us to study the patients under their care, and to Mr David McLeod for help and encouragement in the preparation of this paper. We thank Mr T. Tarrant and the Department of Audiovisual Communications, Institute of Ophthalmology, Judd Street, London, WC1, and Mr K. Sehmi for their help with the illustrations, and Miss Christine Giffen and Miss Heather Lucas, who kindly provided valuable secretarial assistance.

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Silicone oil injection in the treatment of massive preretinal retraction. II. Late complications in 93 eyes

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SUMMARY Long-term assessment of eyes in which silicone oil injection had been used in the treatment of retinal detachment with massive preretinal retraction was undertaken in 92 consecutive patients. While a high incidence of complications, particularly cataract, was confirmed, this study showed that they were probably caused not by any toxic effect of silicone oil but by obstruction of normal metabolic exchange at the silicone-tissue interface. The incidence of complications causing deterioration of vision or serious symptoms was not found to be high, and navigating vision was well preserved.

The use of silicone oil injection in the treatment of massive preretinal retraction is associated with a high incidence of late complications (Watzke, 1967; Okun, 1968; Cockerham *et al.*, 1969; Grey and Leaver, 1977), yet the importance of these has not been established. Furthermore, it is accepted that the use of this technique in the treatment of otherwise irreversible retinal detachments is justified when the fellow eye is impaired or at risk (Okun, 1968; Mukai *et al.*, 1972; Grey and Leaver, 1977). The purpose of this paper is to report the late complications of silicone oil injection and to assess their effect on visual function. A single case report is presented to provide histological evidence of the changes associated with intraocular silicone oil.

Patients and methods

Ninety-three eyes in 92 consecutive patients who had undergone silicone oil injection (Grey and Leaver, 1979) and for whom follow-up data were available for 1 year or more after surgery were assessed. Documentation was undertaken at 1, 2, 3, and 4 years after surgery, and assessment included a careful examination of the cornea, anterior chamber angle, lens, and retrolental space with slit-lamp biomicroscopy and gonioscopy. Electrodiagnostic studies were undertaken in 13 cases.

Results

INCIDENCE OF LATE COMPLICATIONS

Cataract. After 1 year 30 out of 61 phakic eyes (49%) exhibited some degree of clinically recognisable lens changes which were not present before surgery. The incidence of this finding rose to 74% of 35 eyes assessed at 2 years and was 65% in 25 eyes after 3 years (Table 1). The type and extent of the lens changes varied from mild posterior subcapsular opacities to dense opacities of the lens nucleus and cortex (Fig. 1).

Table 1 *Cataract*

At 1 year	(61 eyes)	30	(49%)
At 2 years	(35 eyes)	26	(74%)
At 3 years or more	(20 eyes)	13	(65%)

Table 2 *Glaucoma*

Pathogenesis	*Phakic (7 eyes)*	*Aphakic (7 eyes)*	*Total (14 eyes)*
Chronic simple	2	2	4
Closed angle	2	3	5
Oil in angle only	2	1	3
Unknown	1	1	2

Glaucoma. Persistently raised intraocular pressure of more than 22 mmHg was recorded in 14 (7 phakic and 7 aphakic) out of 93 eyes (15%), and in 9 of these fine globules of silicone oil were found in the anterior chamber angle. In 3 eyes this was the only abnormality identified, while in the remaining 11 a history of pre-existing chronic simple glaucoma was found in 4, angle closure was present in 5, and in 2 there was no identifiable abnormality (Table 2).

Gonioscopic findings. Minute globules of silicone

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oil were found in the angle of the anterior chamber superiorly in 26 (43%) phakic and 11 (34%) aphakic eyes examined after 1 year or longer. Closure of the drainage angle ranging from 10 to 100% was found in 27 eyes; in 12 the extent of closure was greater than 50%, and in 5 of these fine particles of silicone oil were present in the anterior chamber.

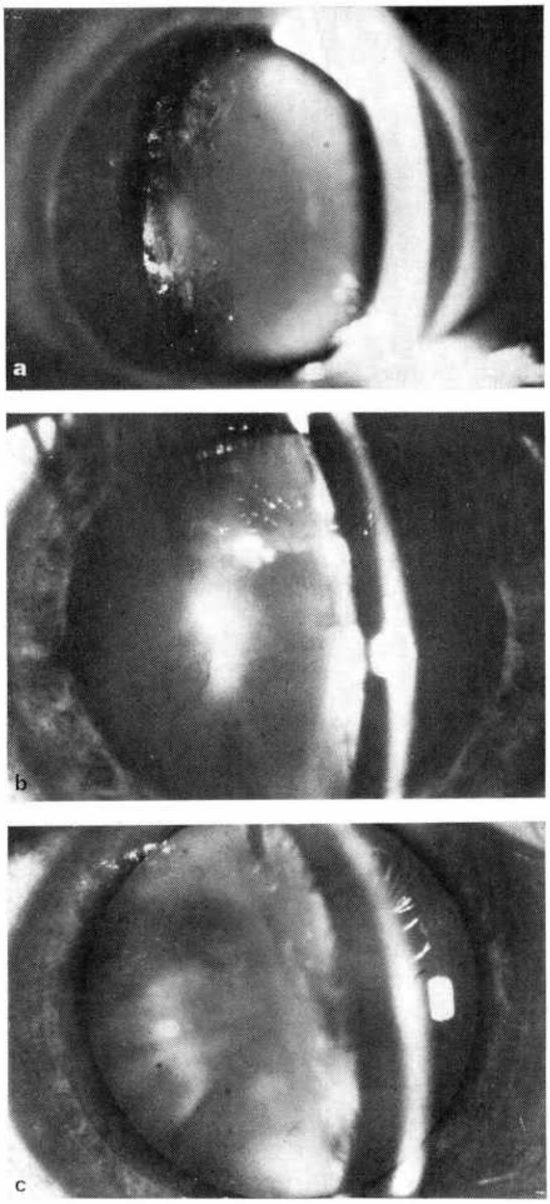

Fig. 1 (a) *Posterior subcapsular lens opacities 2 years after silicone oil injection.* (b) *Opacities in the nucleus and cortex 18 months after silicone oil injection.* (c) *Dense cataract 2 years after silicone oil injection*

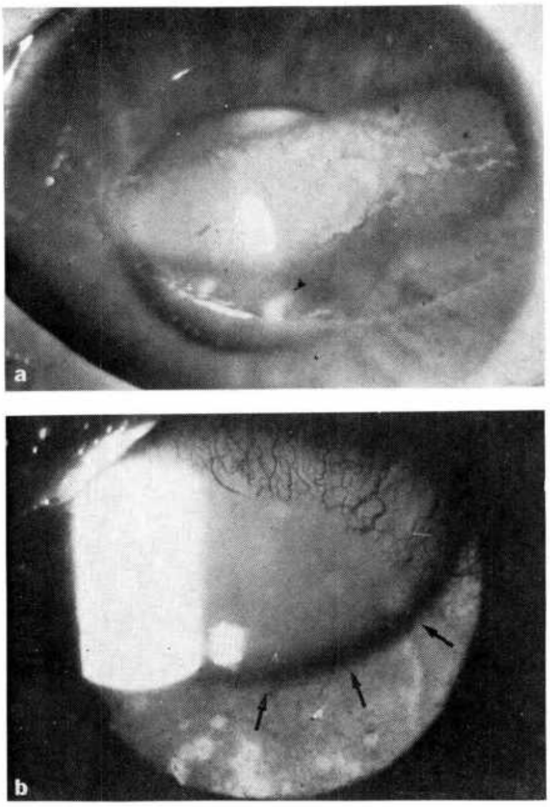

Fig. 2 (a) *Band-shaped keratopathy 1 year after silicone oil injection.* (b) *Vascularised keratopathy 18 months after silicone oil injection. Arrows indicate the lower margin of the silicone oil globule in the anterior chamber*

Keratopathy. Band-shaped and/or vascularised keratopathy (Fig. 2) was identified in 5 aphakic and 1 phakic eye. Of these 6 eyes 5 had a single large oil bubble in the anterior chamber (Fig. 3*a*), but in 1 the corneal changes were associated with a history of multiple needlings for congenital cataract, and no oil was present in the anterior chamber (Table 3). In the single phakic eye oil entered the anterior chamber during a trabeculectomy operation 2 years after silicone oil injection (Fig. 3*b*).

EFFECTS OF LATE COMPLICATIONS IN ANATOMICALLY SUCCESSFUL CASES

In 51 eyes in which the retina remained attached throughout the follow-up period the early postoperative acuity was maintained or improved in 34 (67%), while in 17 (33%) it deteriorated. Of the 34 eyes in which the initial postoperative vision was maintained or improved 38% had late complications, whereas in the 17 which deteriorated the comparable figure was 76% (Fig. 4).

ELECTRODIAGNOSTIC STUDIES IN ANATOMICALLY SUCCESSFUL CASES

In 13 eyes in which the retina was reattached after silicone oil injection electroretinography was carried out; 9 showed positive responses, though the potential was much less than in normal eyes, and in 4 there was no response. The electroculogram done in 10 cases showed no light rise in 9 and a good light rise (200%) in 1, but with a very low standing potential.

Table 3 *Keratopathy*

Oil in anterior chamber	*Phakic (1 eye)*	*Aphakic (5 eyes)*	*Total (6 eyes)*
Present	1*	4	5
Absent	0	1	1

*Occurred after trabeculectomy

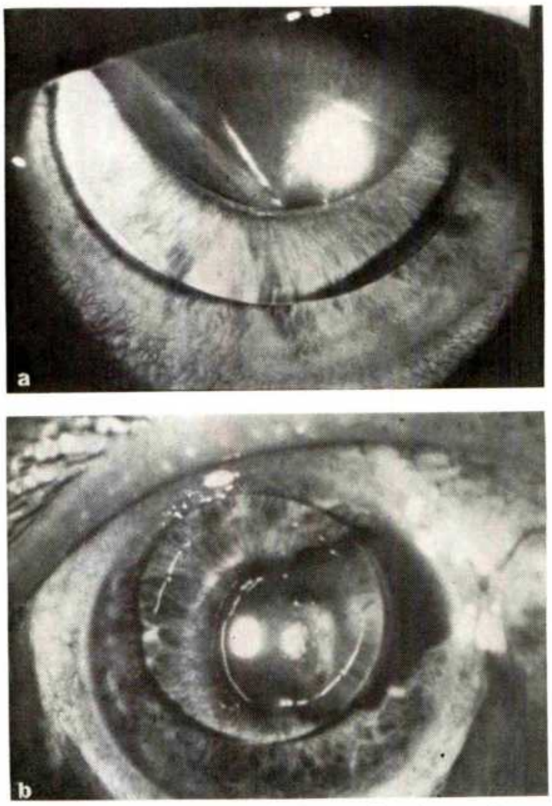

Fig. 3 (a) *Large globule of silicone oil in the anterior chamber 1 year after silicone oil injection in an aphakic eye.* (b) *Large silicone oil globule in the anterior chamber of a phakic eye following trabeculectomy 2 years after the injection of silicone oil*

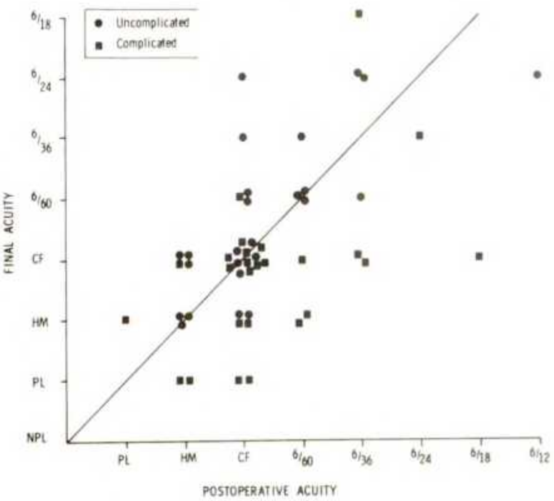

Fig. 4 *Scattergram comparing the early postoperative to the final visual acuity in 51 eyes in which the retina remained attached throughout the follow-up period. Points above the line show an improvement during the postoperative period, points on the line show no change in the postoperative vision, and points below indicate a deterioration*

Case report

A 33-year-old woman was admitted to Moorfields Hospital in March 1974 with a bullous retinal detachment in the right eye associated with a large operculated U-tear. Intraocular pressures were 14 mmHg in each eye. The following day she underwent a buckling procedure with local explant and cryotherapy, during which the sclera was perforated accidentally by a suture needle, causing escape of subretinal fluid but without haemorrhage. After this procedure the retina failed to flatten because the tear was not adequately closed by the buckle, and 2 weeks later the Silastic sponge explant was replaced, with subsequent retinal reattachment. Visual acuity was reduced to counting fingers at 1 m, due to previous macular detachment.

In July 1974 the retinal detachment recurred in the right eye, with evidence of massive preretinal retraction. On 29 July 4 ml of silicone oil (1000 cSt) was injected into the retrohyaloid space via the pars plana. Subretinal fluid was drained, and the retina was reapposed to the pigment epithelium. After this procedure the visual acuity improved to 6/60 in the right eye.

No complications were noted until October 1976,

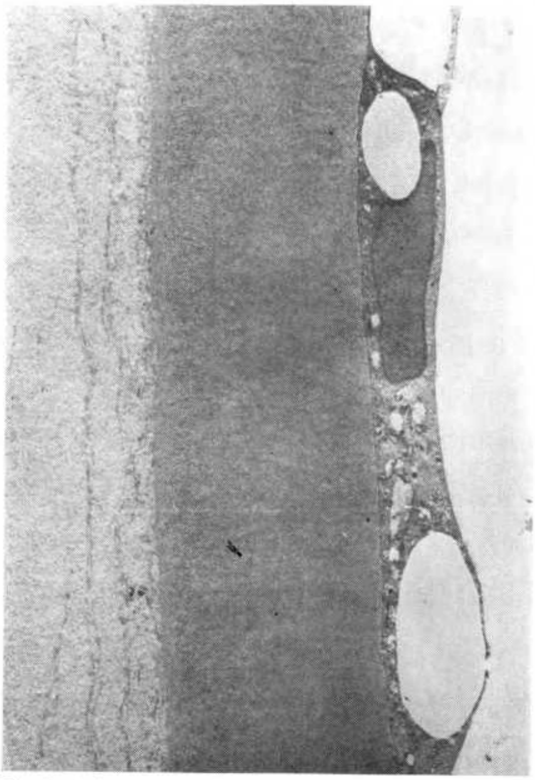

Fig. 5 *Electron micrograph of posterior cornea showing endothelial cells which contain large intracytoplasmic vacuoles filled with flocculent material. Glutaraldelyde/OsO_4/uranyl acetate/lead citrate (× 3000)*

when she was observed to have an intraocular pressure of 46 mmHg in the right eye and there was a fine emulsion of silicone oil globules in the anterior chamber; the intraocular pressure in the left eye was 24 mmHg at this time. In November 1976 trabeculectomy was carried out in the right eye, and the oil globules were washed out of the anterior chamber. This procedure was uneventful, and after surgery the intraocular pressure was well controlled. During the subsequent months, however, the right eye became soft, rubeotic, and painful, with recurrent hyphaemata, and in March 1977 the right eye was enucleated.

HISTOLOGICAL FINDINGS

Light microscopy. Sections taken from the cornea, anterior chamber angle, lens, and retina of the enucleated eye were examined by light microscopy. Vacuoles of varying sizes which had presumably been occupied by silicone oil were found in the corneal endothelium, trabecular meshwork, on the anterior and posterior surfaces of the lens, and on the retina, both lying free and within the cytoplasm of macrophages.

ELECTRON MICROSCOPY

Cornea. The cytoplasm of some endothelial cells showed large membrane-bound vacuoles which were either empty or contained granular flocculent material and which probably represented phagocytic activity (Fig. 5). Occasional cells showed early degenerative change in the form of mitochondrial swelling, but advanced necrosis was not seen, and there was no apparent disturbance of Descemet's membrane or the deep stromal lamellae.

Trabecular meshwork. The trabeculae appeared to be normal with prominent long-spaced collagen and an intact endothelial lining. The spaces between

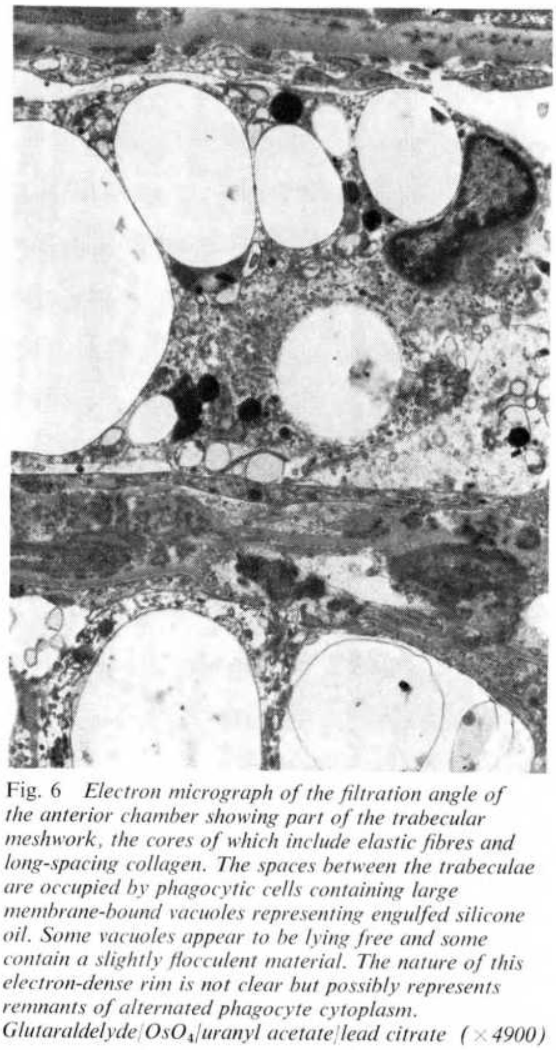

Fig. 6 *Electron micrograph of the filtration angle of the anterior chamber showing part of the trabecular meshwork, the cores of which include elastic fibres and long-spacing collagen. The spaces between the trabeculae are occupied by phagocytic cells containing large membrane-bound vacuoles representing engulfed silicone oil. Some vacuoles appear to be lying free and some contain a slightly flocculent material. The nature of this electron-dense rim is not clear but possibly represents remnants of alternated phagocyte cytoplasm. Glutaraldelyde/OsO_4/uranyl acetate/lead citrate (× 4900)*

the meshwork, however, were largely obliterated by macrophages containing empty vacuoles of varying size (Figs. 6 and 7). Also present were rounded accretions of flocculent material surrounded by a slightly more electron-dense rim. The rim did not have the appearance of a cell membrane, and, although its precise significance is unknown, similar structures have been described following experimental intravitreal oil injection in the monkey (Mukai *et al.*, 1975).

Lens. Anteriorly there was no detectable abnormality apart from phagocytes containing empty vacuoles adherent to the capsule (Fig. 8). Similar cells were also seen posteriorly, where in addition there were foci of subcapsular lenticular fibre degeneration manifested as swelling with increased electron lucency (Fig. 9). Vacuoles comparable to those seen in macrophages and in the filtration angle were not present within the substance of the lens.

Retina. The retinal surface was covered by a generally homogeneous layer of moderate electron density embedded in which were spheroidal droplets of greater electron density. Deep to this acellular covering there were aggregates of phagocytic cells containing vacuoles of varying size identical to those previously described in the anterior segment (Fig. 10). A few similar electron-lucent vacuoles were present in the inner layers of the retina, deep to the inner limiting membrane, and appearing to be both intra- and extracellular. Such vacuoles were generally smaller than those on the surface of the retina, while those which were intracellular were within Müller's cells.

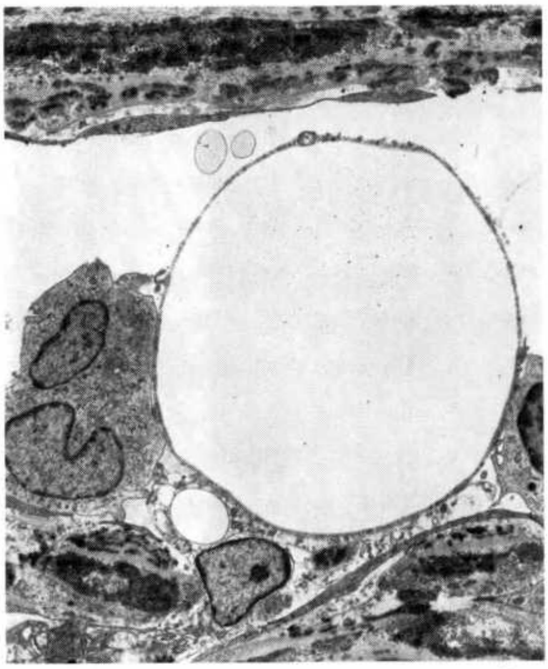

Fig. 7 *Trabecular meshwork showing phagocytic cells between the collagenous trabeculae. One such cell contains a massive vacuole covered for the larger part by a narrow rim of cytoplasm only. Other free-lying small globules of flocculent material with a slightly more electron-dense rim are also present. Glutaraldelyde/OsO_4/uranyl acetate/lead citrate (× 3000)*

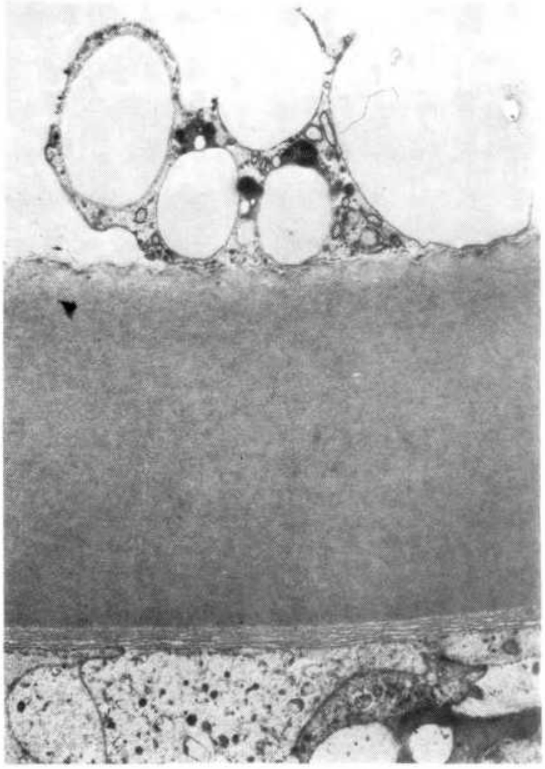

Fig. 8 *Part of a phagocytic cell with large vacuolar inclusions presumed to represent engulfed silicone oil attached to the anterior lens capsule. The capsule, basement membrane, and epithelium of the lens, however, show no evidence of infiltration by the oil. Glutaraldelyde/OsO_4/uranyl acetate/lead citrate (× 4900)*

Discussion

Although the results of this study confirm the findings of previous workers that silicone oil injection is associated with a high risk of complications (Watzke, 1967; Okun, 1968; Cockerham *et al.*, 1969; Grey and Leaver, 1977), many of these could be expected to occur after unsuccessful conventional procedures and in association with long-standing

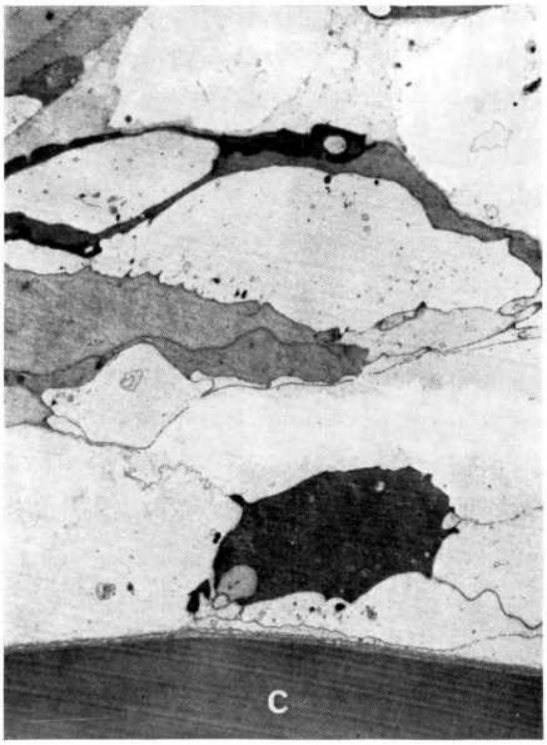

Fig. 9 *Some of the posterior fibres of the lens are degenerate and unusually electron-lucent (C = posterior lens capsule). Glutaraldelyde/OsO$_4$/uranyl acetate/lead citrate (× 2400)*

complicated retinal detachments. Close analysis of our findings shows that the improvement in visual function associated with successful reattachment of the retina by this method is maintained in the majority of cases (Fig. 4) and that complications, when they occur, do not necessarily cause progressive visual deterioration.

In common with those of Okun (1968) our findings confirm that cataract is the commonest late complication of silicone oil injection (Table 1), but the lens changes are not usually dense enough to cause loss of navigating vision. No evidence of silicone oil particles within the substance of the lens was demonstrated in our specimen. The lens changes appeared to be due not to any toxic effect of silicone oil on the lens fibres but to deposition of silicone-laden macrophages on the surface of the lens capsule preventing normal metabolic exchange (Figs. 8 and 9).

The presence of silicone oil particles in the angle of the anterior chamber was a common finding, but the incidence of raised intraocular pressure was not high and did not usually appear to be related to the presence of oil in the angle, an observation previously reported by Watzke (1967), while in several cases raised pressure was present in this or the fellow eye before surgery. Fine particles of silicone oil may be released into the anterior chamber by rupture of silicone-oil-laden macrophages which have migrated forwards from the bubble present in the retrohyaloid space. This finding is as common in phakic as it is in aphakic eyes, and it seems probable that the presence of a large number of such particles within the trabecular meshwork could cause obstruction to aqueous outflow. In this series, however, while more than half of the eyes with raised intraocular pressure had oil particles in the anterior chamber angle, in two-thirds of these there was angle closure or evidence of pre-existing glaucoma.

In a few aphakic eyes in which there was a dehiscence in the vitreous remnant a large globule of

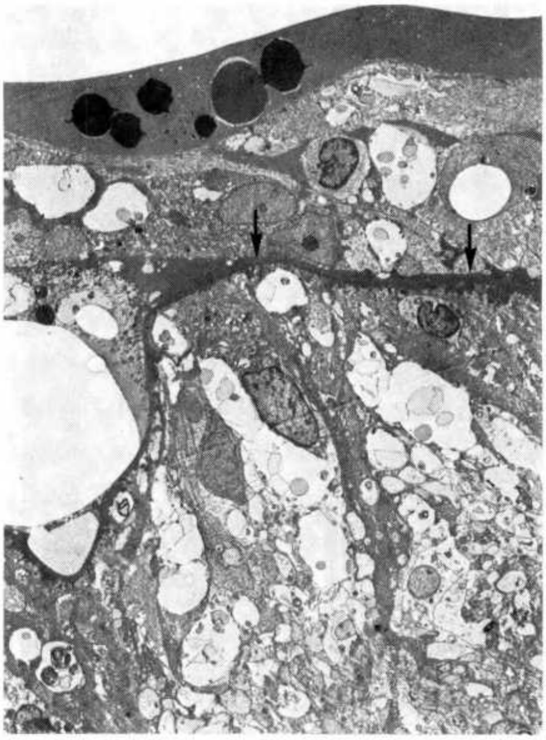

Fig. 10 *Electron micrograph of the inner retina, the inner limiting membrane of which (arrows) is overlaid by a homogeneous layer of moderate electron density containing globules of greater density and phagocytic cells containing vacuoles comparable to those seen in the trabecular meshwork and elsewhere. Vacuoles, some apparently empty and others containing amorphous material, are also present within the nerve-fibre layer of the retina. Glutaraldelyde/OsO$_4$/uranyl acetate/lead citrate (× 1500)*

silicone fluid came forward into the anterior chamber after surgery, causing a severe and often painful keratopathy (Fig. 2). This complication can also occur occasionally in phakic eyes undergoing surgical procedures subsequent to the injection of silicone oil (Fig. 3*b*) or after trauma (Sugar and Okamura, 1976).

In contrast the commoner finding of a fine emulsion of silicone oil particles in contact with the corneal endothelium did not cause any clinically recognisable corneal disease. The histological findings in our case showed that small silicone oil particles were taken up by the endothelial cells but did not migrate into the corneal substance or cause pathological changes in Descemet's membrane or the stroma. We therefore presume that the adverse effect of the large silicone oil bubble was due to its obstructive effect, like that seen on the anterior and posterior lens surfaces.

While no toxic effect of silicone oil was demonstrated, the case for attributing cataract, glaucoma, and keratopathy to a purely obstructive mechanism is strengthened by the fact that these complications can be satisfactorily managed by standard methods. In a recent review of complications after silicone oil injection (Leaver *et al.,* 1978) we reported the results of treatment in 25 eyes in which successful management by extracapsular cataract extraction, medical treatment of glaucoma, and removal of large oil globules from the anterior chamber was accomplished in most cases.

Histological examination of the retina showed fine silicone oil particles within the retinal substance like those shown by Mukai (Mukai *et al.,* 1972). However, in common with those seen elsewhere in this specimen, these particles appeared to be contained within macrophages and glial cells rather than within the neurosensory elements of the retina, the latter appearing to be essentially unaffected.

In only 4 eyes in which the retina remained reattached throughout the follow-up period and in which the initial visual improvement was not maintained was there no evidence of cataract, glaucoma, or keratopathy (Fig. 4). Previous workers have used the electroretinogram response in animal eyes filled with silicone oil both to support (Lee *et al.,* 1969) and to disprove (Armaly, 1962) the hypothesis that late deterioration of vision after successful reattachment of the retina is sometimes caused by silicone retinopathy.

However, the results of electrodiagnostic tests in eyes in which the vitreous has been replaced by an electrical non-conductor cannot be compared to those obtained from intact eyes (Arden, personal communication). In this study we were able to demonstrate a positive ERG response in the majority of eyes in which this test was undertaken, although the potentials were low compared with the normal and the electro-oculogram showed a light rise in one instance only. It would be unwise to draw any conclusions from these results, and, although the possibility of silicone retinopathy exists, we did not find firm evidence from which to make this diagnosis.

We conclude that, while the technique of silicone oil injection is associated with a high risk of long-term complications, particularly cataract, the severity of these and their effect on the maintenance of visual improvement after surgery is frequently minimal, while navigating vision is well preserved. Furthermore, when late complications require treatment, this can be successfully accomplished by standard methods.

We are grateful to Mr Lorimer Fison and the consultant surgeons at Moorfields Hospital who kindly allowed us to study the patients under their care and to Mr David McLeod for help and encouragement in the preparation of this paper. We thank Mr T. Tarrant and the Department of Audiovisual Communications, Institute of Ophthalmology, Judd Street, London, WC1, and Mr K. Sehmi for their help with the illustrations. Miss Christine Giffen and Miss Heather Lucas kindly provided valuable secretarial assistance.

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Vascular opacification and leakage in X-linked (juvenile) retinoschisis

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SUMMARY A 22-year-old man had X-linked retinoschisis with extensive vascular sheathing in the posterior pole and dendritic opacified retinal vessels in the periphery. Detailed fluorescein angiographic studies were performed. In the far periphery areas of capillary nonperfusion were seen. Sluggish circulation was present in the majority of dendritic opacified vessels in the areas of schisis. Late staining of the disc and posterior arteries and veins was noted. Scattered intraretinal fluorescein leakage was present even in clinically nonschitic retina, which suggests that the vascular changes may precede the retinoschisis. The patient's half-brother also had X-linked retinoschisis, but the schisis and the vascular changes were much less prominent. Although the retinal vascular changes with X-linked retinoschisis are similar to those seen with the Favre-Goldmann syndrome, a differentiation of the two diseases can be made by family studies, the presence or absence of nyctalopia, examination of the macular areas, measurement of dark adaptation, and electroretinogram determinations.

Juvenile retinoschisis is an X-linked recessive vitreoretinal dystrophy with a high degree of penetrance and variable expressivity (Deutman, 1977). Ophthalmoscopic findings include foveal changes (cystoid spaces with a bicycle-spoke pattern of radial striae), vascular sheathing, peripheral retinoschisis, vascularised veils in the vitreous, occasional vitreous haemorrhage, pigmentary changes in the fundus, and in some cases white dendritic arborescent structures in the peripheral retina. Previous fluorescein angiographic studies (Krause *et al.*, 1970; Burns *et al.*, 1971; Constantaras *et al.*, 1972; Tasman, 1975; Harris and Yeung, 1976) of X-linked retinoschisis have concentrated primarily on changes in the posterior pole, while the vascular changes in the peripheral retina have received scant attention (Ewing and Ives, 1969; Ewing and Cullen, 1972; Tasman, 1975). We recently examined 2 brothers with X-linked retinoschisis. One had large areas of retinoschisis with unusually prominent dendritic structures (Cibis, 1965) in the retinal periphery and marked vascular sheathing in the posterior pole. The other had small areas of peripheral retinoschisis with early vascular opacification. Our findings on ophthalmoscopy and fluorescein angiography show that retinal vascular changes can be a prominent feature of the clinical picture of X-linked retinoschisis.

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Case reports

CASE 1

A 22-year-old man of Mexican descent came to the Illinois Eye and Ear Infirmary in September 1977 with a complaint of bilateral progressive decrease in vision of about 10 years' duration. Previously his vision was said to have been normal, but no previous ophthalmological evaluations had been performed. The patient also complained of mild photophobia, but he specifically denied night blindness. His general medical health was excellent, and there was no family history of ophthalmological problems, except for one half-brother whose case is described below (Case 2). No other family members were available for examination.

Ophthalmological examination showed a best corrected visual acuity in the right eye of counting fingers (+5·00S +1·25 cx 175°), left eye 20/200 (+2·25S +3·25 cx 170°); 15° of right exotropia were seen with an afferent pupillary defect on the right. Slit-lamp biomicroscopy of the anterior segment and applanation tonometry were normal. No cataracts were present. Ophthalmoscopy disclosed normal optic discs, but there was marked vascular sheathing in the posterior pole, the arteries being slightly more involved than the veins (Fig. 1). In the right eye the vascular sheathing continued inferiorly to a large area of retinoschisis (Fig. 2). The schisis involved the entire inferotemporal quadrant. The remainder of the fundus, including the posterior pole, had a recticular texture (Fig. 3). The macula showed a characteristic bicycle-spoke appearance with coalescence of many of the cystoid spaces.

Examination of the fundus on the left showed 2 large highly elevated schisis cavities, 1 inferior and 1 superotemporal. The inferior cavity occupied most of the inferior periphery and extended from near the ora serrata to within 4 disc diameters of the optic nerve and macula. The reticular pattern found in the right eye was much less prominent and was present only at the posterior edges of the schisis cavities. The macular area showed cystoid changes but without the coalescence seen in the right eye (Fig. 4). A large inner-layer retinal hole was seen in the area of schisis in the left eye superotemporally (Fig. 5).

The periphery of both eyes in areas of retinoschisis showed a prominent dendritic pattern of whitish opacified vessels (Figs. 2 and 5). These vessels appeared to represent small arterioles and venules as well as capillaries. The changes were most pronounced in the midperiphery and were less prominent anterior to the equator and at the posterior margin of the schisis. A mild degree of vessel opacification was apparent, however, along the posterior margins of the schisis extending into apparently nonschitic retina (Fig. 6). The majority of opacified vessels were seen in the inner layer of schisis, but in some areas white vessels were noted in both layers of the schisis cavity (Fig. 5).

Dark adaptation testing showed a normal cone final threshold. The final rod threshold was raised 0·5 log unit at 15° superior to the fovea, testing with a 2° white test target using the Goldmann-Weekers dark adaptometer. Colour vision testing (Helve, 1972) with the Farnsworth-Munsell 100-hue test showed a blue-yellow defect in the left eye. The electroretinogram (ERG) was obtained by techniques previously described (Fishman *et al.*, 1977). The photopic response in the left eye showed normal amplitudes and implicit times. The right eye amplitudes were minimally subnormal with normal implicit times. The scotopic response bilaterally produced a normal a-wave amplitude, while the b-wave amplitude was significantly reduced, giving a negative type response. A flicker response produced with red light at 30 cycles per second showed a subnormal response in the right eye and a normal response in the left eye. A flicker response produced with a low-intensity blue stimulus showed moderately subnormal amplitudes in each eye, with the right eye being depressed more than the left.

Fluorescein angiography was performed in the macula and periphery of both eyes. Angiography confirmed that the white dendritic lesions were opacified retinal vessels (Figs. 7*a*–7*c*). The circulation in the vessels was markedly delayed. Anterior to the vascular opacification areas of extensive capillary nonperfusion were apparent (Fig. 7*c*). A few of the opacified vessels were also not perfused, though the majority of them were patent. Posterior to the schitic areas patchy staining of vessel walls with some intraretinal leakage of fluorescein was present in some areas (Fig. 8). Views of the posterior pole showed no definite retinal leakage into the cystoid spaces in the maculae (Figs. 9*a* and 9*b*). Mild disruption of the pigment epithelium was apparent in the right macula with window defects visible in two areas. Other areas of pigment disruption were present near the disc in the right eye and in the periphery. The walls of large arteries and veins and the discs in both eyes stained with fluorescein in late views (Fig. 9*b*).

CASE 2

This patient is the 30-year-old half-brother of Case 1. They have the same mother but different fathers. The patient was asked to come in for ophthalmological examination, though he had no visual complaints. When queried, however, he did state that his right eye was 'not as good' as his left eye. He denied night blindness.

Ocular examination showed a best corrected visual acuity in the right eye of 20/200 (+4·75S +2·00 cx 150°), left eye 20/70+ (plano +1·50 cx 70°). The extraocular muscle balance and the pupillary responses were normal. Slit-lamp biomicroscopy of the anterior segment and applanation tonometry showed nothing abnormal.

Fundus examination on the right disclosed a normal disc and a bicycle-spoke pattern of macular cystoid changes. No posterior vascular sheathing was noted. The peripheral retina showed areas of mild pigment disruption and other areas with a peculiar sheen. No elevated schisis was present, but 2 small (1 disc diameter) areas of opacified capillaries were found, 1 inferior at 6 o'clock and 1 superotemporal at 9.30 o'clock.

Ophthalmoscopic examination of the left eye again showed the characteristic macular cystoid changes. The remainder of the retina was normal with the exception of a temporal semi-circular ridge of tissue that represented the remnant of a schisis cavity (Fig. 10). A small area of opacified vessels was seen at the inferior border of this ridge. A

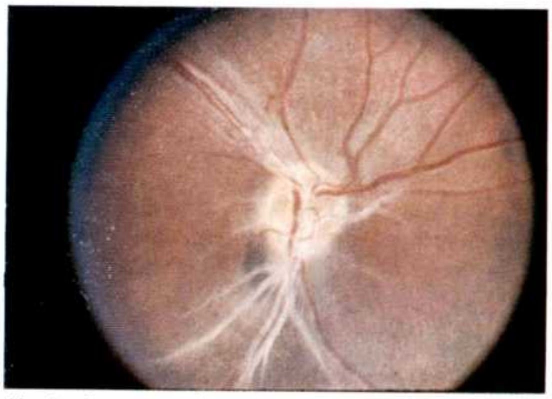

Fig. 1 *Posterior pole, right eye, Case 1, shows markedly sheathed retinal vessels. Arteries are more involved than veins*

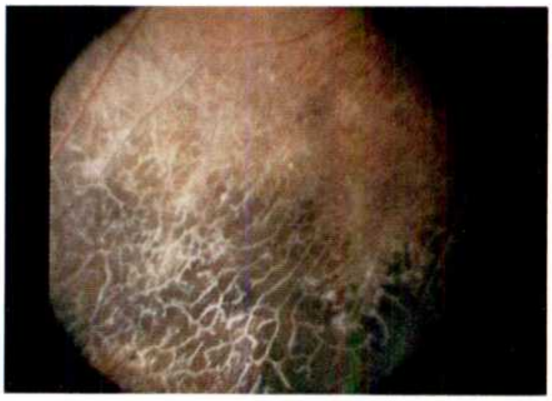

Fig. 2 *Right eye, Case 1, showing inferotemporal retina. Large raised schisis cavity is seen with opacified retinal vessels and pigment clumping*

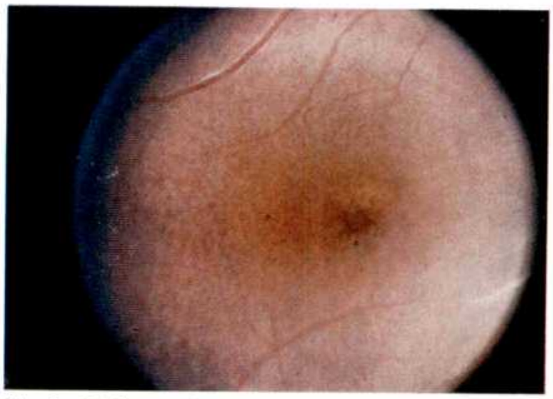

Fig. 3 *Right eye, Case 1. Foveal area shows confluence of many cystoid spaces. Remainder of posterior pole shows reticular pattern that is most marked temporal to macula*

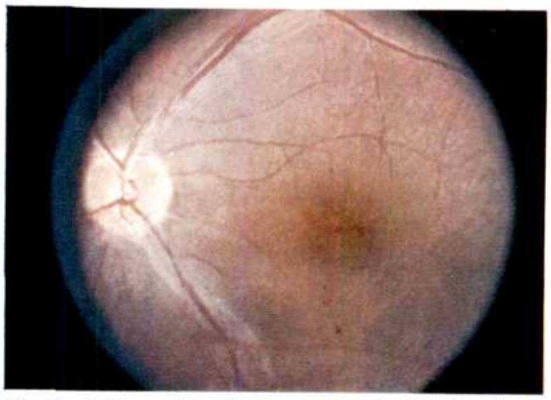

Fig. 4 *Left eye, Case 1, showing classic bicycle-spoke pattern of cystoid spaces in macula. Reticular pattern seen in right eye is absent*

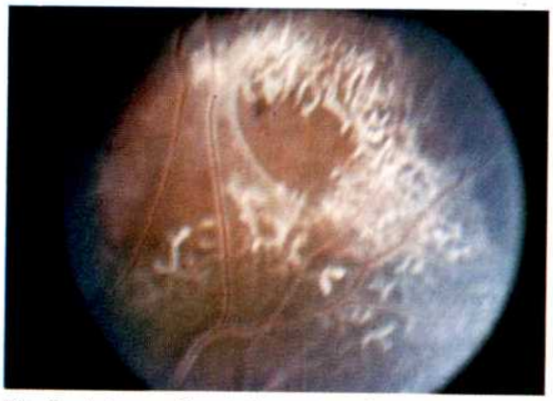

Fig. 5 *Left eye, Case 1. Large inner layer retinal hole is visible in area of schisis. Opacified retinal vessels can be identified in both inner and outer retinal layers*

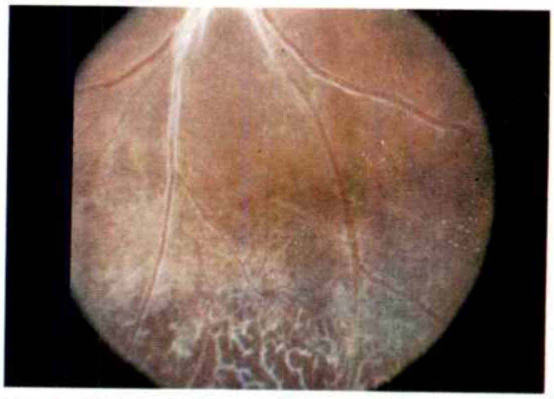

Fig. 6 *Right eye, Case 1, shows extension of vascular opacification into flat apparently nonschitic retina*

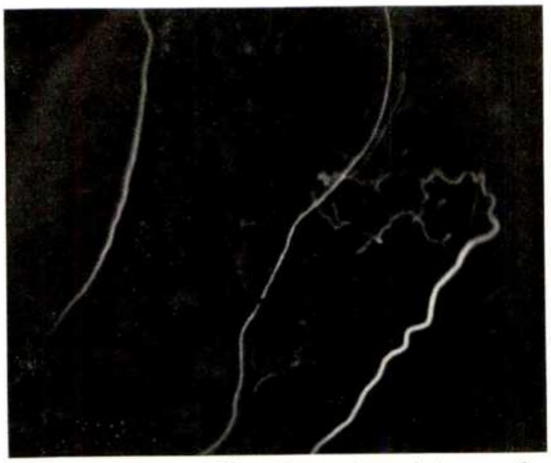

Fig. 7a *Sequence of filling of retinal vessels in area of schisis. Arterial phase shows very slow filling of vessels*

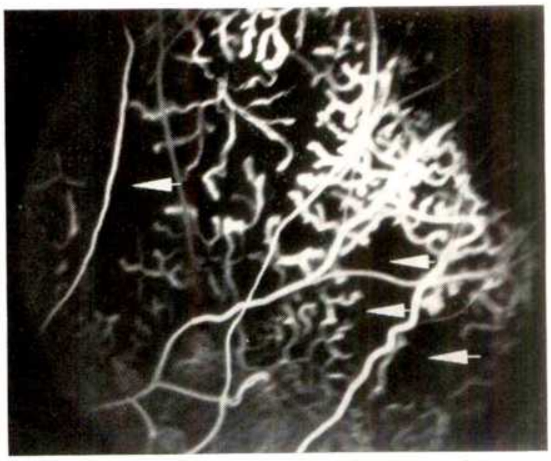

Fig. 7b *Venous phase shows that arborescent white structures seen in Fig. 5 are retinal vessels. Some areas of capillary dropout are present (arrows)*

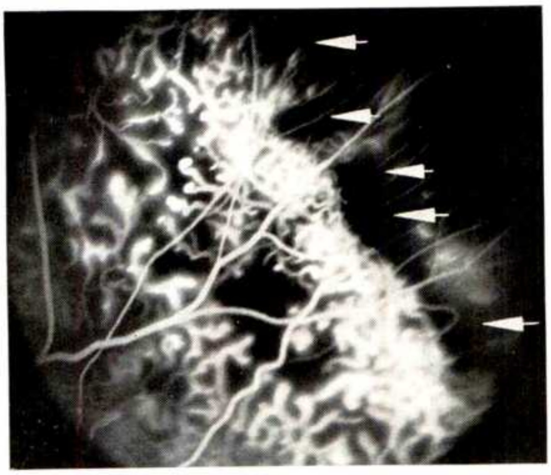

Fig. 7c *Slightly more anterior view shows extensive capillary dropout (arrows) anterior to opacified vessels. Staining of opacified vessel walls is apparent with some intraretinal leakage of fluorescein*

remnant of the inner layer of schisis was present in the vitreous.

Fluorescein angiography showed no macular leakage in either eye but intraretinal leakage and capillary nonperfusion temporally in the left eye in the area of schisis. The ERG demonstrated selective depression of the b-wave under photopic and scotopic conditions. The scotopic changes were more pronounced, however.

Discussion

Congenital retinoschisis was first described concurrently in 1932 by Thomson (1932) and Anderson (1932). Thomson's report included a description of the characteristic radial spokes in the macula as well as peripheral pigment clumping and retinal elevation. Jager (1953) published the first account in which splitting of the inner retinal layers was identified as the origin of the vascular veils in the vitreous. He termed this process retinoschisis. Subsequent histopathological studies (Yanoff *et al.*, 1968; Manschot, 1972) have suggested that the splitting occurs mainly in the nerve fibre layer.

Fluorescein angiography has been used to study the macula in X-linked retinoschisis. These studies have in general shown no leakage of fluorescein into

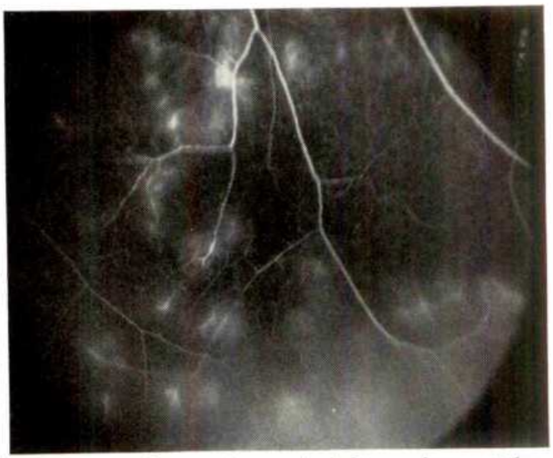

Fig. 8 *Late phase angiogram in right eye shows patchy vessel wall staining and leakage at margin of schisis in clinically nonschitic retina (above) as well as schitic retina (below)*

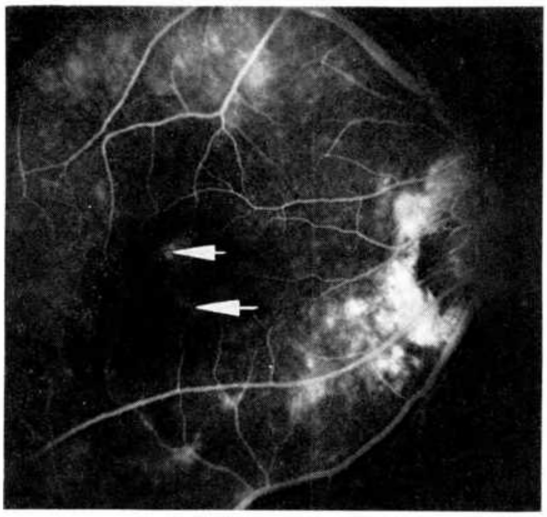

Fig. 9a *Posterior pole, right eye, Case 1. Angiogram shows pigment disruption under inferotemporal vessels with 2 small areas of pigment irregularity under macula (arrows). No leakage into cystoid spaces is present*

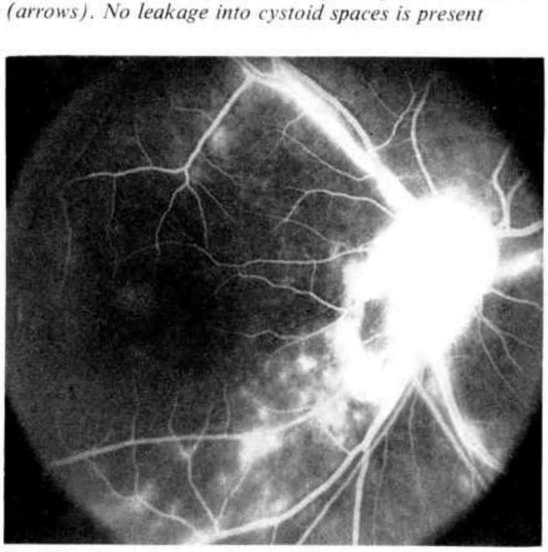

Fig. 9b *Late phase angiogram shows prominent staining of disc and large vessels, especially veins*

the cystoid spaces in the macula (above). However, in some cases faint pooling of fluorescein has been found (Ewing and Cullen, 1972). Both our cases showed classic bicycle-spoke patterns in the macula with no fluorescein leakage. In both eyes of Case 1 there was prominent staining of the optic disc and large vessel walls with some intraretinal leakage of dye in the posterior pole. Disruption of the retinal pigment epithelium under the macula and near the disc was present in the right eye only.

Previous authors have commented briefly on fluorescein angiography of the periphery of patients with X-linked retinoschisis. Tasman (1975) noted pigment epithelial atrophy in the areas underlying a vitreous veil. Ewing and Ives (1969) and Ewing and Cullen (1972) mentioned that the dendritic structures in the periphery were patent vessels that fill with fluorescein. They noted delayed circulation in many cases and suggested that the vessels may in some instances be neovascular (Ewing and Ives, 1969) and that the fundus picture in X-linked retinoschisis could resemble Eales's disease. The first case presented here shows vividly that these white dendritic structures are opacified vessels. In areas of advanced schisis a few of the dendritic vessels were not perfused. Elsewhere a slow filling of opacified vessels was noted. No neovascularisation was seen. Presumably vessels in both the deep and superficial capillary networks of the retina were opacified, as in some areas dendritic structures were visible in both the inner and outer layers of the schisis cavity. At the anterior margins of the schisis large areas of capillary nonperfusion were present. The retinal capillaries in these areas seemed to have totally disappeared. At the posterior margins of the schisis early vessel opacification and some fluorescein leakage were noted; these changes extended into flat nonschitic retina. Case 2 also showed opacified

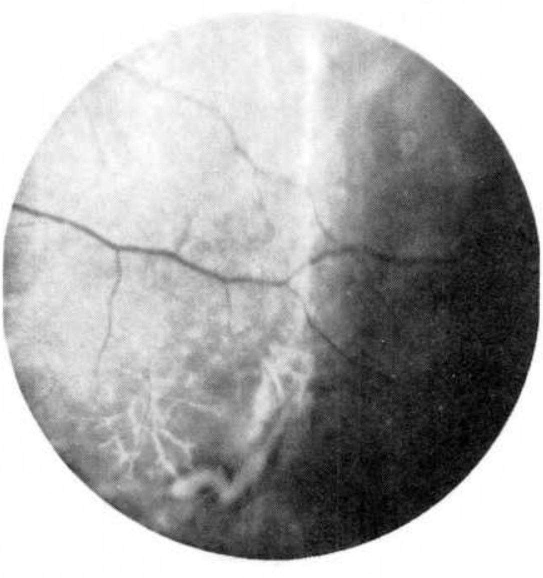

Fig. 10 *Temporal periphery, left eye, Case 2, shows ridge of retinoschisis with early vascular opacification along inferior margin of ridge*

vessels. However, the changes were subtle and could have been overlooked without careful examination of the retinal periphery. This case also showed the characteristic depression of the b-wave of the ERG, which can be seen with even minimal peripheral retinoschisis.

Retinal vascular leakage and opacification have also been described in association with the Favre-Goldmann syndrome (Fishman *et al.*, 1976). Although the Favre-Goldmann syndrome also shows retinoschisis, it is an autosomal recessive disease characterised by night blindness and photoreceptor degeneration. The presence of vascular leakage and opacification in both these hereditary diseases with retinoschisis is puzzling. It is possible that abnormalities of the retinal circulation could contribute to the development of the retinoschisis. The fact that these areas of retinoschisis are not totally avascular does not detract from this hypothesis. The decreased blood flow in these areas could result in localised ischaemia that might contribute to the resultant separation of the inner from the outer retinal layers. Retinal vascular leakage could also play a role in schisis formation. Conversely, it is also possible that the vascular opacification and leakage are secondary to the retinoschisis, though we believe that this is unlikely, since vascular sheathing and early vessel wall opacification and leakage were seen in our patients and in some patients with Favre-Goldmann syndrome (Fishman *et al.*, 1976) even in areas where no schisis was present. The origin of the vascular changes in these two diseases remains uncertain.

Differentiation of X-linked retinoschisis from the much rarer Favre-Goldmann syndrome is not difficult. Our patients complained of no night blindness (which is an early symptom in the Favre-Goldmann syndrome), and the dark adaptation curve in Case 1 showed only minimal increase of rod final thresholds. In addition the maculae of our patients had the bicycle-spoke pattern characteristic of X-linked juvenile retinoschisis. The macular changes in the Favre-Goldmann syndrome are much more subtle (Fishman *et al.*, 1976). In addition, ERG findings in the Favre-Goldmann syndrome (Fishman *et al.*, 1976) show abnormalities of both the a- and b-waves, often with nondetectable amplitudes. In X-linked retinoschisis ERG abnormalities are limited to depression of the b-wave except in markedly advanced stages. Macular changes similar to X-linked retinoschisis have also recently been reported in a family with familial foveal retinoschisis (Lewis *et al.*, 1977). These patients, however, had normal ERG recordings.

Dr Gerald Fishman performed the electrophysiological measurements, and Mr Norbert Jednock, OP, assisted with the photography.

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British Journal of Ophthalmology, 1979, **63**, 374

Book reviews

Erkrankungen der ableitenden Tränenwege und ihre Behandlung. Ed. HOLGER BUSSE and FRITZ HOLLWICH. Pp. 178. DM44. Ferdinand Enke Verlag: Stuttgart. 1978.

Moderne Probleme der Erkrankungen der Lider und des Tränenapparates. Ed GERD MEYER-SCHWICKERATH and KLAUSE ULLERICH. Pp. 265. DM55. Ferdinand Enke Verlag: Stuttgart. 1978.

These 2 volumes in the popular series Modern Problems of Diseases of the Lids and Lacrimal Apparatus should be read in conjunction. The first volume discusses diseases of the lacrimal system and their management. The anatomy, physiology, and pathology of the lacrimal passages are described in detail and the surgical and medical management of these disorders reviewed for postgraduate students. The book is well illustrated with diagrams and photographs and provides a valuable manual for those embarking on lacrimal surgery.

The companion volume provides 16 articles on a variety of subjects related to problems in the lids and lacrimal passages. They cover surgical and medical topics and are well illustrated. Each paper has a short English summary. Contributions include articles on plastic reconstruction of the lids, ptosis and its management, lid tumours, and problems of tear production and drainage. The postgraduate student and equally the lacrimal surgeon will find this a useful and interesting volume. T. J. FFYTCHE

Neuro-Ophthalmology Update. By J. LAWTON-SMITH. Pp. 396. £37·75. Abacus Press: Tunbridge Wells. 1978.

This text of 369 pages from 51 contributors is liberally illustrated and well indexed. It is concerned with problems which may arise in the consulting room of any practising neuro-ophthalmologist. After an opening chapter by the editor consisting of 35 clinical aphorisms culled from a lifetime of concentrated study there follows 2 chapters on pathological lid retraction, 4 on pupil anomalies, 2 on sixth nerve syndromes, 9 on syndromes of the optic nerve, 2 on orbital disease, 5 on chiasmal syndromes, 6 on computerised axial tomography, and 2 on downbeat nystagmus. There are single chapters on hereditary macular dystrophies, the treatment of syphilis with benzathine penicillin, eye signs in Charcot-Marie-Tooth disease, and treatment of migraine and retinal functional tests.

If a would-be purchaser would like to dip in and taste the excitement and thrill of this evolving subject, a glance at the chapter on the 'Diencephalic syndrome of emaciation in infancy and childhood' or, to take another at random, 'The impossible meningioma syndrome', will surely persuade him that a place must be found for this text on a bookshelf close to his place of work, handy for ready reference.

It would be true to say that the introduction of CAT, ultrasononography, fluorescein angiography, and the recording of visual evoked and other responses has revolutionised the process of diagnosis in neuro-ophthalmology so much so that an older culture may be in danger of dying. This technical leap ahead is comparable to that of radar from astral navigation. It is interesting, however, to note that the editor believes field testing in some chiasmal syndromes is a more revealing and reliable investigation than scanning.

The main problem of neuro-ophthalmological diagnosis in the rich, developed countries is that of selection. Otherwise every patient with a headache is in danger of being submitted at great expense to a battery of tests and therapy administered according to the 'read-out'. The main problem in the poor and developing countries is likely to remain the lack of facilities required to make an accurate and early diagnosis. As half the population of our planet can barely afford a plain *x*-ray, far less a CAT scan, action to alleviate this state of affairs, political rather than medical, might well prove (*pace* the editor's foreword) as propitious as prayer to an omnipresent god. S. J. H. MILLER

Notes

Paediatric ophthalmology

The second congress of the International Society of Paediatric Ophthalmology will be held in Parma, Italy, on 20–24 June 1979. The programme includes topics on environment and the eye, non-chromosomal malformations, inherited errors of metabolism, albinism, phakomatoses, and free communications. For programme correspondence contact Dr Heskel M. Haddad, 1200 Fifth Avenue, New York, New York 10029, USA, or Professor Mario Maione, Department of Ophthalmology, University of Parma, Parma 43100, Italy. For travel arrangements contact Garber Travel, 1406 Beacon Street, Brookline, Massachusetts 02146, USA.

Photobiology

The VIII International Congress on Photobiology will be held in Strasbourg, France, on 20–25 June 1980. Subjects to be discussed include: Spectroscopy, photochemistry of proteins and nucleic acid-protein complexes, photochemistry of nucleic acids, repair of photochemical lesions, radiation-induced carcinogenesis, genetic aspects, photosensitisation, phototherapy, effects of non-ionising radiations on retina and on transparent media of eye. Further details from Dr M. Charlier, Centre de Biophysique Moléculaire, 1A Avenue de la Recherche Scientifique, 45045 Orleans Cedex, France.

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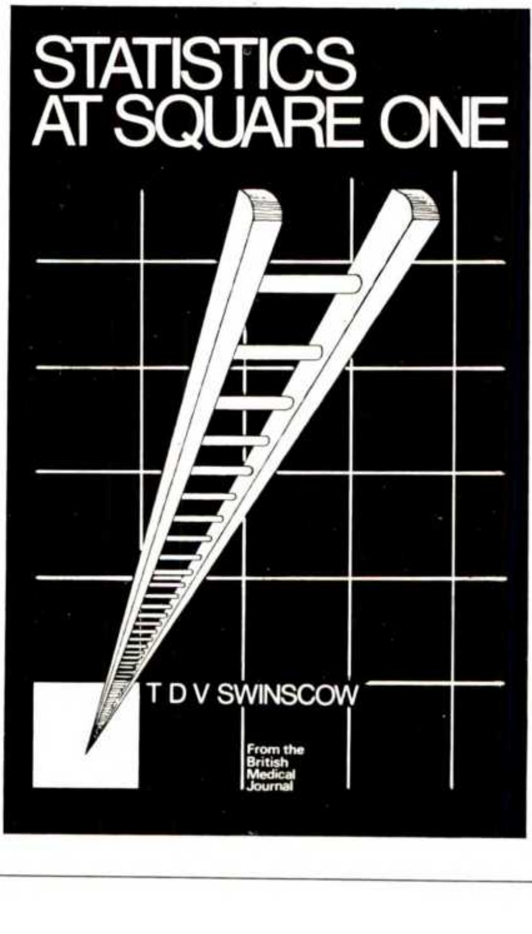

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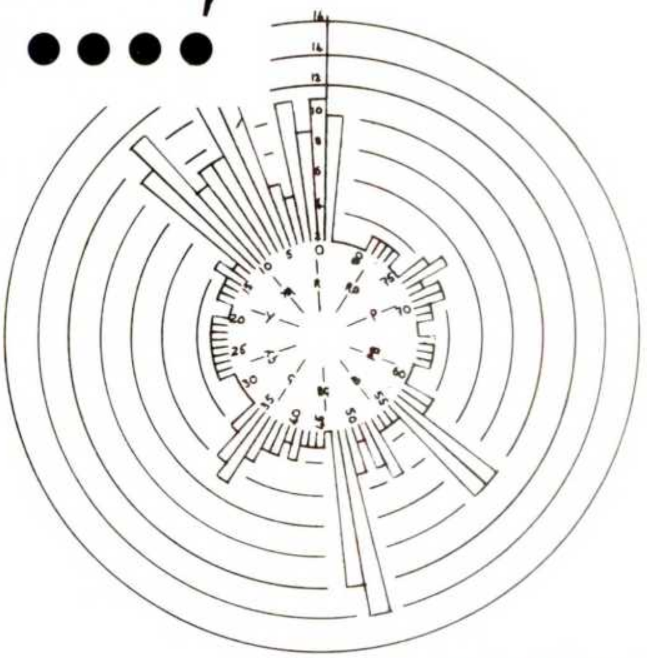

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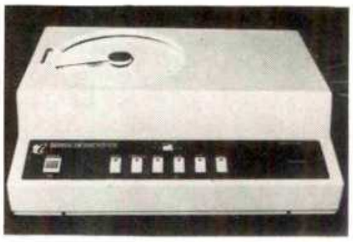

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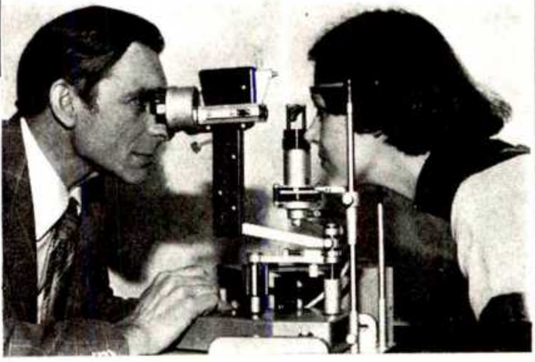

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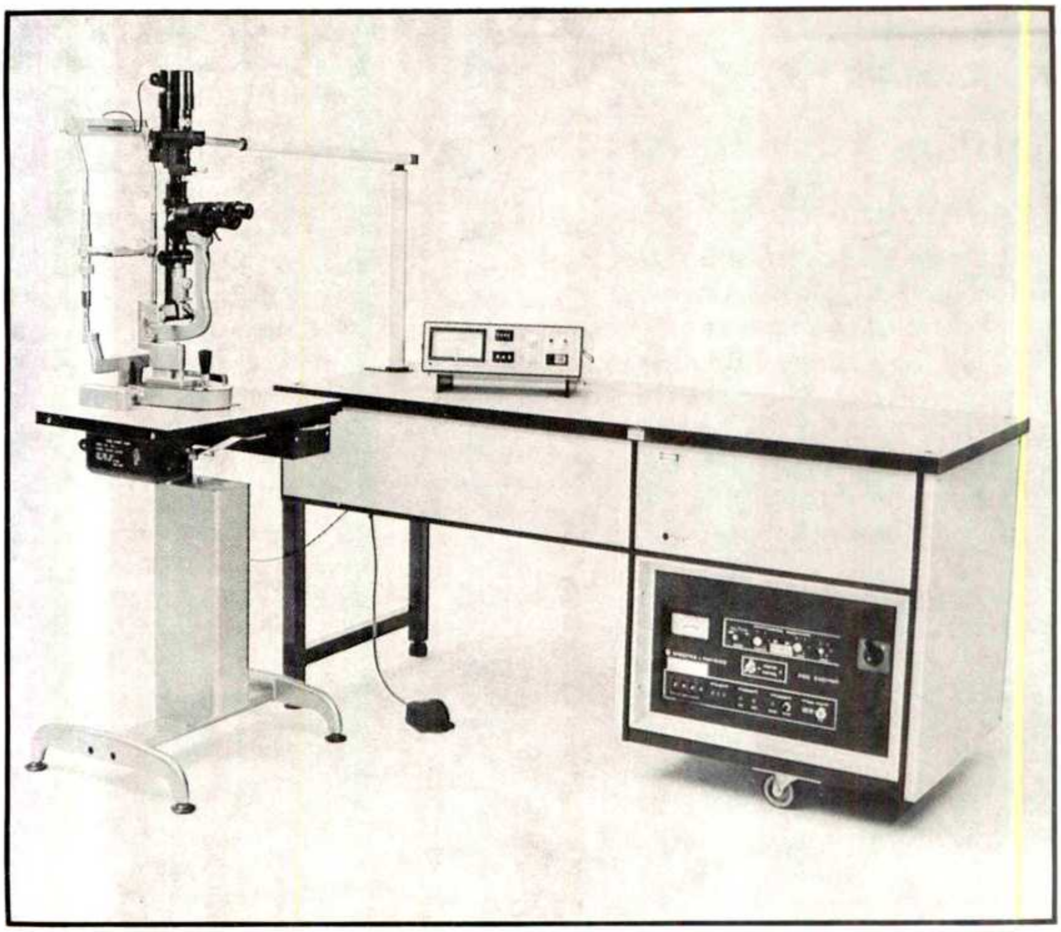

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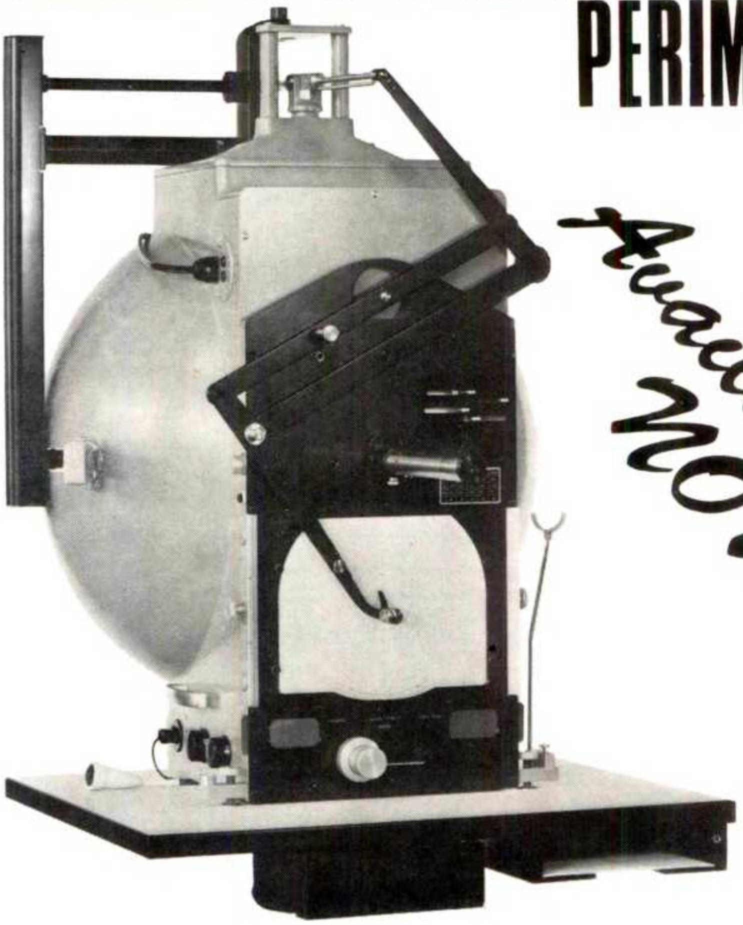

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British Journal of Ophthalmology, 1979, **63**, 375–376

Editorial: Retinal vein occlusion

The clinical features and evolution of retinal vein occlusion have been described in detail in a number of publications during the last few years (Wise *et al.*, 1971; Blankenship and Okun, 1973; Clemett *et al.*, 1973; Kohner and Shilling, 1976; Laatikainen and Kohner, 1976). It has also become evident that central and branch vein occlusion are manifestations of a similar disease process, namely, obstruction to outflow. The differences in the clinical appearances are due to differences in the site of the obstruction.

It is perhaps unexpected that in spite of the detailed clinical observations ranging over several years there should still be uncertainty about the pathogenesis of the lesions. It is to resolve these problems that a large number of animal experiments have been performed, the latest of which are reported in this issue by A. M. Hamilton *et al.* (p. 377), D. A. Rosen *et al.* (p. 388), and D. J. Hockley *et al.* (p. 393).

The aim of the experiments was to establish the evolution and pathogenesis of the lesions seen. How far have they succeeded? The acute features closely resembled retinal branch vein occlusion as seen in man, but the progression of the lesions reproduced the progression in man incompletely. The 2 clinical pictures seen were resolution in some animals, while large and extensive haemorrhages predicted progressive occlusion of capillaries and later large vessel changes. Most disappointing was the absence of preretinal neovascularisation in spite of early, though often transient, intraretinal neo- and revascularisation. Macular oedema was also never observed after the acute stages.

Collateral flow through pre-existing capillary connections occurred immediatedly after occlusion. This flow was not sufficient to maintain normal drainage, and there was marked reduction of blood flow to well below 40% of the original. Large-diameter collaterals mostly lateral to the macula developed, but their efficacy varied in different animals as shown by the variability of blood flow. In some animals normal blood flow was re-established. This, as expected, occurred in those with complete resolution. Resolution often occurred in those animals which developed effective by-pass channels circumventing the occluded segments early on. In animals with large areas of capillary occlusion collaterals in the far periphery of the retina were observed. These were always of very large diameter and once established appeared to function as shunt vessels. Such large peripheral collaterals were never reported in man. Possibly widespread vascular disease prevents their development.

Since large collaterals were present in all animals after the first week, while maximum haemorrhage—indicating maximal non-perfusion of capillaries—occurred during the first week, it is in the early period that the changes are most important. During this period as a result of outflow obstruction there is a rise in intravascular pressure. This results in oedema and even in expulsion of red cells. The endothelial cells are damaged but certainly not disrupted. A vicious circle is then set up. Stagnation of flow causes ischaemia and endothelial cell damage. Raised intravascular pressure expels fluid from the capillaries, retaining formed elements and increasing viscosity. This further reduces flow and further increases ischaemia, until finally there is complete cessation of flow and disintegration of both pericytes and endothelial cells. It is after 24 hours that the large haemorrhages occur. Indeed by the time the haemorrhages are present there is already capillary non-perfusion, which becomes more widespread with time.

A progressive 'ischaemic capillaropathy' is thus produced. Previous work indicates that this occurs after retinal artery occlusion (as expected) and after combined occlusion of artery and vein (Hayreh, 1978) or occlusion of vein and cilioretinal artery (McLeod and Ring, 1976). The papers in this issue of the *BJO* show that it also occurs as a result of *isolated* outflow obstruction.

It is hoped that this finding will finally put an end to the widely held misconception that progressive capillary closure in retinal vein occlusion is due to arterial occlusion, at least of a critical duration (Hayreh, 1965, 1978). Retinal arterial inflow in these experiments was reduced after the vein occlusion, presumably as a result of the increased intravascular pressure, not because of primary arterial disease. Ischaemia is a well recognised feature of retinal vein occlusion. Previous authors (McLeod and Ring, 1976; Laatikainen and Kohner, 1976; McLeod and Kohner, 1978) do not disagree with this finding. They disagree with Hayreh (1978) on the pathogenesis of the ischaemia. These experiments prove them correct.

There are a number of unexplained observations in the work reported. These include apparently normal capillaries and some with actually slit-like opening—as though compressed by oedema. In a condition characterised by intraluminal pressure approaching arteriolar pressure this is difficult to explain. Indeed it is not really clear why in some animals the acute picture resolved rapidly. What makes some capillaries more resistant to raised intravascular pressure and ischaemia than others? Is it only a question of developing adequate collateral flow within the first 24 to 72 hours, before there is irreversible damage to blood vessels, allowing adequate perfusion? Or is it that some capillaries form pinocytic vesicles less readily and thus retain fluid and maintain flow?

The fact that preretinal vessels were never seen and even intraretinal new vessels tended to regress could have been due to the presence of large peripheral collaterals acting as shunt vessels. Many factors in the stimulation and inhibition of new vessel formation are unknown. While these experiments support the importance of 'avascular' retina in new vessel formation, they throw no new light on their pathogenesis.

Finally, have these experiments any relevance to the human disease? Quite correctly the work did not aim at establishing the pathogenesis of retinal vein occlusion. For it would be ludicrous to suppose that acute and complete occlusion of vessels in healthy animals with normal circulation could reproduce the pathogenesis of a disease characterised by widespread vascular disease and slowly developing incomplete vascular occlusion. But as a result of these experiments we understand the development of early lesions better than we did before. However, we get no therapeutic clues and indeed a great many fundamental questions remain unanswered. To answer them we need new ideas and new approaches.

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British Journal of Ophthalmology, 1979, **63**, 377–387

Experimental retinal branch vein occlusion in rhesus monkeys. I. Clinical appearances

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SUMMARY Branch and hemisphere vein occlusion were produced in rhesus monkeys by argon laser photocoagulation. The following observations were made: (1) Immediately after occlusion there was venous dilatation, delayed filling of the artery, delayed drainage by the occluded vein, and capillary leakage. (2) Two patterns of evolution were identified within the first week. In some animals the fundus changes resolved and the retina returned to normal, while in others there was progressive retinal capillary closure. (3) Those animals destined to have capillary closure had diffuse or cluster retinal haemorrhages at 24 hours. (4) Capillary closure took place over 1 week and was usually complete over large areas of retina. (5) Retinal atrophy and major vessel changes occurred over several weeks. (6) Retinal revascularisation occurred in those areas of closure, though this was often limited. It was concluded that the early changes mimicked those seen in human retinal vein occlusion, though persistent retinal oedema and preretinal neovascularisation were not identified.

The morphological changes which follow retinal branch vein occlusion in man have been well documented (Foster-Moore, 1924; Jensen, 1936; Wise, 1957; Gass, 1968; Archer *et al.*, 1974). Occlusion may occur close to the optic disc edge, causing disease in a retinal hemisphere; at a major arteriovenous crossing, resulting in changes within a quadrant; or at a minor crossing, in which case a small sector of the retina is affected. Retinal haemorrhages, infarcts, and oedema may be seen soon after occlusion; capillary closure with new vessel formation and persistent oedema occur as late complications and are largely responsible for persistent visual loss (Archer *et al.*, 1976).

The pathogenesis of these phenomena following venous occlusion have been studied in animal homologues (Becker and Post, 1951; Campbell, 1961; Linner, 1961; Okun and Collins, 1963; Voipio and Riatta, 1964; Mutlu, 1966; Kohner *et al*, 1970; Archer *et al.*, 1974).

In this paper we report the results of a further study which was designed to define in more detail the fundus changes following venous occlusion and in particular to identify those factors which may be more important in the genesis of capillary closure. Flow measurements and histopathological studies were also undertaken and are reported separately (Rosen *et al.*, 1979; Hockley *et al.*, 1979).

Methods

Rhesus monkeys were chosen as the experimental animal because of the close resemblance of the retinal vasculature to that of the human. Forty-five retinal vein occlusions were produced in 31 healthy monkeys of varying age.

ANAESTHESIA

The monkeys were all anaesthetised by intravenous thiopentone (4·6 ml of 2·5% solution) and intubated with a cuffed endotracheal tube; anaesthesia was maintained by oxygen and nitrous oxide in the proportion of 1:2 and fluothane.

PHOTOGRAPHY

Pupillary dilatation was produced with the topical applications of 10% phenylephrine drops and 1% cyclopentolate drops. The cornea was irrigated intermittently with normal saline, a lid speculum being used to maintain good exposure.

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Photographs were taken with a vertically mounted Zeiss (Oberkochen) camera with Kodachrome II for colour photographs and Ilford FP4 for fluorescein angiography. Colour and fluorescein photographs were taken several days prior to occlusion and then at intervals after occlusion. Fluorescein angiograms were taken after the injection of 1 ml of 10% solution of sodium fluorescein through a scalp vein needle in a superficial leg vein.

PHOTOCOAGULATION

The argon laser (Coherent Radiation 800) was chosen to produce the occlusion because it was possible to place high-energy burn of small diameter accurately and directly on a retinal vein with the minimum amount of heat diffusion to the surrounding retina, thus minimising the effects on the adjacent retinal vessels. The argon laser beam was delivered through a vertically mounted Zeiss slit lamp, so facilitating its application on the anaesthetised monkey. The laser was directed through a Worst unflanged scleral contact lens, with normal saline between the lens and the cornea.

METHODS OF OCCLUSION

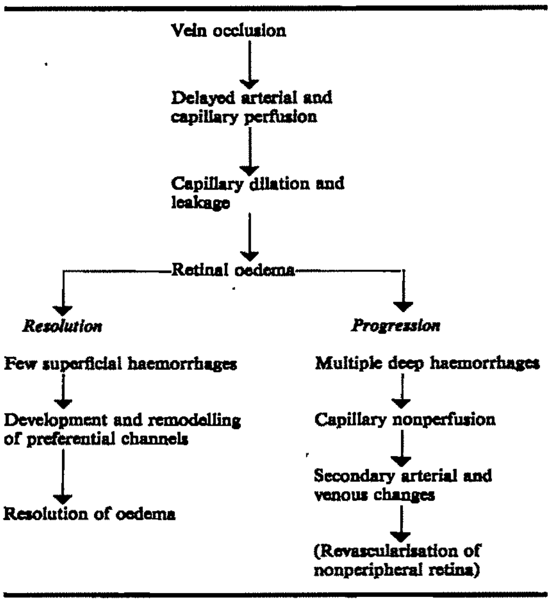
The type and position of the vessel for occlusion was selected prior to the occlusion by examination of fluorescein angiographs. The site chosen for occlusions was well away from neighbouring arteries, and at least 1 disc diameter in length of vein was required for application of the laser. It was found that occlusion of the vein was greatly facilitated by intravenous injection of 1 to 2 ml of 10% sodium fluorescein just before the start of laser application. During this injection the site for occlusion was once more examined and finally confirmed to be free of adjacent arterioles. Argon laser energy was then applied to the vein with either the 50- or 100-µm spot size, an exposure of 0·20 second, and a power setting of 100 to 450 mW. A segment of vein and the immediately adjacent pigment epithelium was blanched by low-intensity burns, and then with increasing power the segment of the vein furthest from the optic disc was occluded. Laser was then applied to the more proximal part of the vein. The end point of laser application was when the occluded segment appeared either salmon pink or white in colour. Finally total occlusion and the absence of patent small vessels adjacent to the occlusion was confirmed by a further injection of fluorescein.

The maximum power required to produce an occlusion never exceeded 450 mW. The number of burns required to effect occlusion was similar in all the large veins occluded, but in the 2 macular tributary veins much less laser energy was required.

The site of the vessel occluded varied. In 2 cases small macular tributaries were chosen; the remainder were either hemisphere or quadrant tributaries.

In 11 monkeys the vein reopened and was reoccluded by further photocoagulation within 1 week. The duration of occlusion was calculated from the time of the permanent occlusion.

Table 1 *Summary of changes following vein occlusion*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Resolution
Progression
Few superficial haemorrhages
Development and remodelling of preferential channels
Resolution of oedema
Multiple deep haemorrhages
Capillary nonperfusion
Secondary arterial and venous changes
(Revascularisation of nonperipheral retina)

Results

A total of 45 occlusions in 31 monkeys were produced, comprising small tributary occlusions (2), branch vein occlusions (14), and hemisphere vein occlusions (29). The details of animals and the lengths of follow-up are shown in Table 1.

The morphological changes and the subsequent outcome were similar irrespective of whether the occlusion was a tributary, a branch vein, or a hemisphere vein occlusion. In view of this the results are not subdivided into these groups (Table 2).

ACUTE STAGE (1 TO 24 HOURS)

Immediately after occlusion there was a marked dilatation of the vein peripheral to the site of occlusion with narrowing and occasionally collapse of the vein proximal to the occlusion. Veins showed increased tortuosity, and there were arteriovenous crossing changes, the angle between the artery and vein at arteriovenous crossing points becoming much more acute (Fig. 1).

Haemorrhages were not a prominent feature immediately after occlusion. In 1 eye (M9) there

Table 2 *Results of occlusion (key to abbreviations at end of Table)*

Eye number	*Vein occluded*	*Period of observation after final occlusion*	*Comment*
1	RSTBVO	1 h 15 min	Slight retinal oedema, deep haemorrhages, no capillary closure
2	LSHVO	1 h 30 min	Retinal oedema + + + no haemorrhages, fluorescein leakage from capillaries and terminal venules + + +, capillary and terminal venular dilatation, no closure
3	RIHVO	2 h	Retinal oedema + + +, no haemorrhages, fluorescein leakage from capillaries and terminal venules + + +, capillary and terminal venular dilatation, no closure, immediate delay in filling of affected half of retina, early capillary colaterals temporal to the macula
4	RSHVO	2 h	Retinal oedema + + +, small deep haemorrhage below and nasal to macula, fluorescein leakage from capillaries and terminal venules + + +, capillary and terminal venular dilatation, no closure, immediate delay in filling of affected half of retina, early capillary collaterals temporal to macula
5	RSHVO	2 h	Retinal oedema + + +, few scattered superficial haemorrhages, fluorescein leakage, no closure
6	RIHVO	2 hr	Retinal oedema + + +, no haemorrhages, fluorescein leakage + + +, capillary and terminal venular dilatation, no closure
7	RIHVO	2 h 30 min	Retinal oedema + + +, no haemorrhages, fluorescein leakage + + +, capillary and terminal venular dilatation, no closure
8	LIHVO	2 h 30 min	Retinal oedema + +, no haemorrhages, focal capillary and terminal venular leakage, capillary and terminal venular dilatation, no closure
9	RSTBVO	3 h	Vitreous haemorrhage shortly after occlusion, nil else seen
10	RSTBVO	3 h	No retinal oedema, no leakage, capillary and terminal venular dilatation, no closure
11	LIHVO	3 h 30 min	Retinal oedema + +, no fluorescein photographs
12	RIHVO	4 h	Retinal oedema + +, few scattered superficial haemorrhages below macula, capillary and terminal venular leakage dilatation, no closure, delayed filling of affected half of retina
13	LIHVO	4 h	Retinal oedema + +, no fluorescein photographs
14	RIHVO	5 h 30 min	Retinal oedema + +, few superficial haemorrhages, capillary and terminal venular leakage + + +, dilatation, capillary closure, immediate delay in filling of affected half of retina, reversal of flow in major vessels
15	RSHVO	7 h	Retinal oedema + +, few superficial retinal haemorrhages, no fluorescein photographs
16	LIHVO	24 h	Retinal oedema + +, preferential haemorrhage at macula, a few scattered haemorrhages, capillary and terminal venule leakage, dilatation, no capillary and terminal venule closure
17	LSTBVO	2 days	Retinal oedema +, haemorrhages temporal to macula, no fluorescein photographs
18	LSTBVO	3 days	Retinal oedema +, extensive haemorrhages and cotton-wool spots, capillary and terminal venule leakage, dilated capillaries, capillary closure
19	LSTBVO	5 days	Retinal oedema + +, scattered haemorrhages, capillary and terminal venular leakage + +, dilated capillaries, collaterals larger than capillaries, temporal to macula, no closure
20	LSTBVO (macular tributary spared)	5 days	Retinal oedema +, scattered haemorrhages temporal to macular, capillary and terminal venular leakage +, dilated capillaries, no closure, collaterals temporal to macula
21	LIHVO	6 days	Retinal oedema + +, extensive haemorrhages, haemorrhages at the site of occlusion and at macula, no fluorescein photographs
22	LIHCO	7 days	Retinal oedema + +, extensive retinal haemorrhages, capillary and terminal venular leakage + +, dilated capillaries and capillary closure, very slow flow in veins with granular flow, leakage from large vein
23	LSHVO	7 days	Retinal oedema + + +, extensive haemorrhage, cotton-wool spots, capillary and terminal venule leakage + + +, dilated capillaries, capillary closure, dilated capillaries temporal to macula
24	L Small macular tributary	7 days	Retinal oedema +, multiple superficial haemorrhages, no fluorescein photographs
25	L Small macular tributary	7 days	No fluorescein photographs
26	LSTBVO	7 days	Retinal oedema + + +, multiple massive haemorrhages, multiple areas of capillary nonperfusion, collaterals temporal to macula
27	LSTBVO	7 days	Few retinal haemorrhages, no fluorescein photographs

Continued

Table 2 *continued*

Eye number	*Vein occluded*	*Period of observation after final occlusion*	*Comment*
28	LSTBVO	14 days	After 6 days no retinal oedema and multiple haemorrhages lateral to macula, ? capillary and terminal venular closure, after 14 days unchanged, but no capillary closure
29	LITBVO	14 days	No retinal oedema, preretinal haemorrhage lateral to macula, capillary and venular dilatation, capillary closure + +
30	RIHVO	14 days	At 7 days no retinal oedema, multiple haemorrhages, capillary and terminal venular dilatation, no leakage, no capillary closure, marked delay in arterial filling, at 14 days appearance unchanged, well-formed collaterals temporal to macula
31	LSHVO	14 days	No haemorrhages, capillary and terminal venular dilatation, no leakage, no closure, large collateral formation
32	LIHVO	14 days	No oedema, extensive haemorrhages and cotton-wool spots adjacent to site of occlusion, capillary and terminal venular leakage, large areas of peripheral capillary nonperfusion
33	RIHVO	14 days	3 days after occlusion retinal oedema + + +, extensive deep haemorrhages, capillary nonperfusion + + +, 1 week after occlusion appearance unchanged but no oedema and veins seen as white lines, 2 weeks unchanged appearance but large-diameter collaterals temporal to macula nasally
34	LSHVO	21 days	No retinal oedema, extensive deep haemorrhages and preretinal haemorrhage, nonperfusion peripherally + + +
35	LSTBVO	21 days	No retinal oedema, multiple haemorrhages, 1 CWS large diameter, collaterals temporal to macula, no capillary closure
36	LSTBVO	21 days	No retinal oedema, haemorrhages and dilated capillaries temporal to macula
37	LIHVO	28 days	At 2 days retinal oedema + + +, scattered haemorrhages, 2 CWS near macula, leakage from capillaries and terminal venules + + +, no capillary closure, delayed perfusion of affected hemisphere, at 7 days no retinal oedema, marked collateral temporal to macula, at 28 days no oedema, well established large-diameter collaterals temporal to macula
38	RSHVO	28 days	No retinal oedema, multiple haemorrhages and CWS, capillary and terminal venule dilatation + +, no leakage, large-diameter collaterals lateral to macula and in nasal periphery, sheathing and narrowing of arteries, pallor of superior half of optic disc
39	RSHVO	28 days	At 2 days retinal oedema + + +, multiple haemorrhages and CWS At 28 days no retinal oedema, multiple haemorrhage, capillary closure + +, large-diameter collaterals lateral to macula, sheathing and narrowing of arteries, pallor of superior half of optic disc
40	RSHVO	28 days	7 days extensive haemorrhages 28 days no retinal oedema, multiple haemorrhages, extensive peripheral closure
41	LIHVO	35 days	2 days, retinal oedema, multiple haemorrhage, capillary and terminal venular leakage, capillary closure 7 days, appearance unchanged 35 days, no oedema, multiple haemorrhages, capillary closure + +, venous and arterial narrowing and sheathing
42	LIHVO	42 days	7 days, retinal oedema, few haemorrhages, capillary and terminal venule dilatation and leakage + + 28 days, widespread capillary and terminal venule dilatation, no capillary closure, venous sheathing and arterial narrowing 42 days, appearance unchanged, pallor of lower half of disc
43	LIHVO	56 days	28 days, extensive haemorrhages and CWS, sheathing of retinal veins and arteries, capillary closure + + + 35 days, large preferential haemorrhage at macula, corkscrew collaterals temporal to macula, large vein leaks as it passes through an area of capillary nonperfusion 56 days, as above, intraretinal new vessel formation, beading of veins and extensive collaterals, and widespread vascular sheathing and occlusion
44	LIHVO	56 days	7 days, multiple haemorrhages and CWS, capillary dilatation and leakage from terminal venules and veins, capillary closure + + 35 days, intraretinal new vessels with leakage from tip of growing vessels, large areas of capillary closure, occlusion of veins and arteries 56 days, regression of intraretinal new vessels, progressive retinal vascular closure, large collateral vessels formation
45	LSTBVO	63 days	7 days, multiple haemorrhages, capillary closure + + 14 days, widespread capillary closure, peripherally extensive collateral 63 days, remodelling collaterals, intraretinal new vessel formation

Key to abbreviations: R = Right. L = Left. STBVO = Superior temporal branch vein occlusion. ITBVO = Inferior temporal branch vein occlusion. SHVO = Superior hemisphere vein occlusion. IHVO = Inferior hemisphere vein occlusion. CWS = Cotton-wool spots

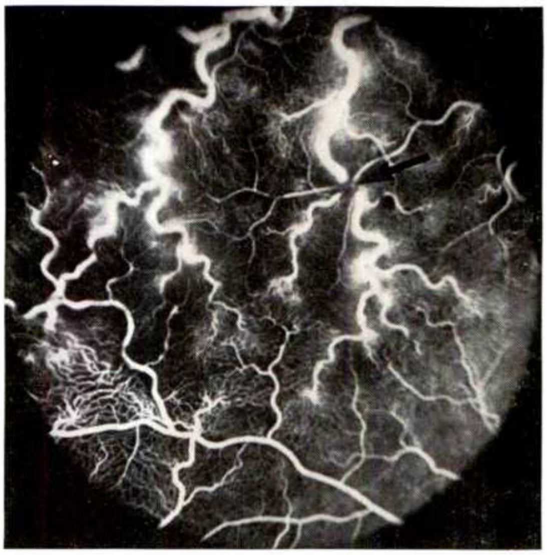


Fig. 1 *Fluorescein angiogram of the horizontal raphe temporal to the macula showing acute angle of arteriovenous crossing, with compression of the vein (arrowed)*

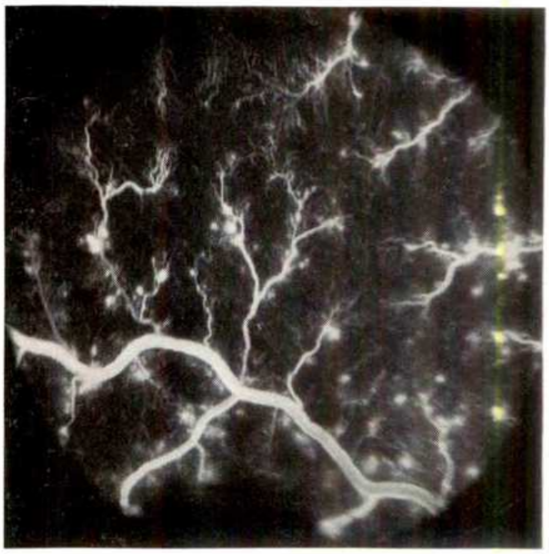


Fig. 2 *Late stage of a fluorescein angiogram to show leakage of dye from the venular end of the capillaries and capillary dilatation*

was a massive vitreous haemorrhage at the time of the occlusion due to inadvertent coagulation of the dilated distal segment of the vein. The few haemorrhages that occurred were superficial, flame-shaped, and were usually close to the site of occlusion (Nos. 1, 4, 5, 12, 14, 15, 16).

Within minutes of the occlusion the retina within the territory of venous drainage became swollen, fluorescein angiography showed delayed appearance of dye in arterioles supplying the affected area, and there was prolonged transit time in the retina drained by the occluded vein (Nos. 3, 4, 12, 14, 30, 37). The capillaries in the distribution of the occluded vein were dilated, and within 5 minutes of fluorescein injection there was dye leakage from the dilated retinal capillaries and terminal venules (Fig. 2). (Nos. 2, 3, 4, 5, 6, 7, 8, 11, 12, 14, 15, 16, 17, 18, 29, 36, 45). In only 1 monkey's eye (No. 10) was there capillary dilatation without leakage.

The retinal oedema persisted for 24 hours in most animals, and limited oedema was still present at 7 days in some. In no monkey was there persistent macular oedema.

Within hours of the occlusion the capillaries in the horizontal meridian between the affected and unaffected quadrants became dilated; this phenomenon was more obvious temporal to the macula than nasal to the optic disc (Fig. 3). Reversal of flow in larger veins was sometimes demonstrated (No. 14) owing to the flow of fluorescein through the preferential channels temporal to the macula (Fig. 4). In only 1 monkey eye (No. 14) with a hemisphere occlusion was capillary closure demonstrated within 24 hours of occlusion. This occurred 5½ hours after occlusion, and the capillary nonperfusion was confined to the area below and temporal to the macula

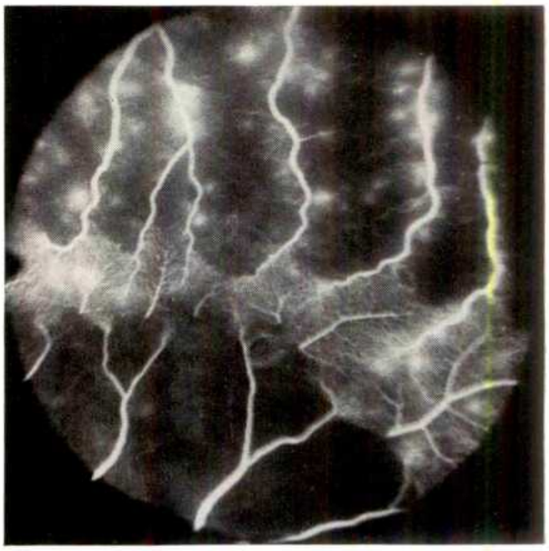


Fig. 3 *Fluorescein angiogram to show dilated capillaries in the horizontal raphe temporal to the macula conveying fluorescein from the occluded to the unoccluded quadrants of the retina*

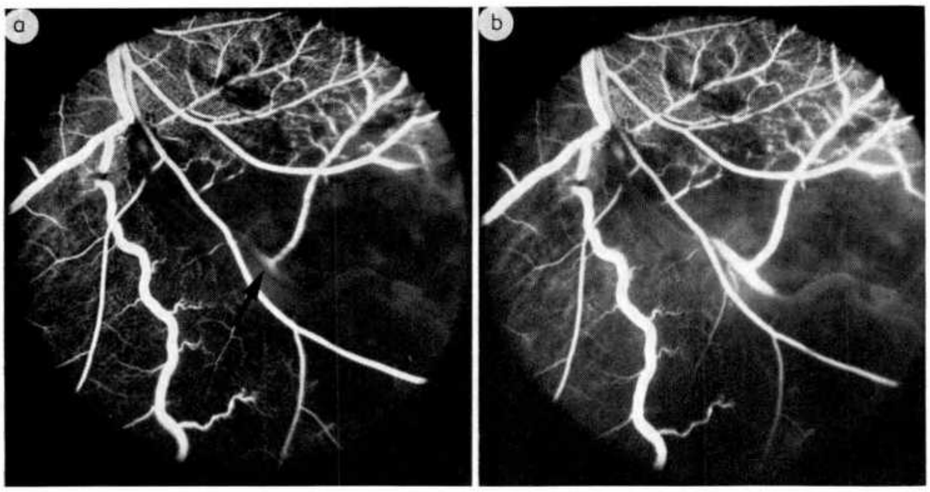


Fig. 4 a and b *Fluorescein angiograms to show reversal of flow in major retinal vein following occlusion (arrowed)*

The subsequent pattern of retinal changes following vein occlusion fell into two broad groups. In the first there was complete resolution of the changes identified whilst in the second there was progression characterised by capillary closure and retinal atrophy. These two patterns of evolution will be described separately.

RESOLUTION OF DISEASE AFTER 24 HOURS

Retinal oedema slowly subsided, and the amount of leakage from the terminal venules and capillaries diminished. In this group of monkeys the retinal haemorrhages, which were few and superficial (Nos. 16, 17, 19, 20, 24, 27, 42), were gradually absorbed over the subsequent weeks. The fine multiple collateral channels which had formed between the affected quadrants were replaced by larger, fewer, and sometimes tortuous blood vessels temporal to the macula (Fig. 5). These collateral channels did not leak fluorescein at any stage.

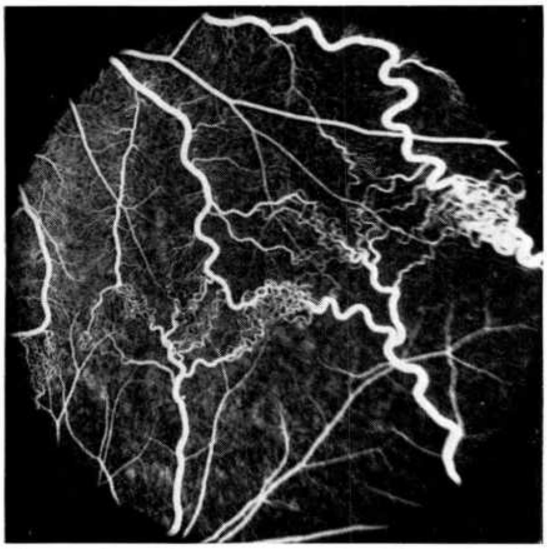


Fig. 5 *Fluorescein angiogram showing dilated channels in the horizontal raphe temporal to the macula; some channels are multiple and fine, whereas others are coarser and less numerous*

The capillary pattern appeared normal on fluorescein angiography, and there was no evidence of of any secondary arteriolar or venular changes. In this group the nerve fibre layer remained intact, and there was no pallor of the optic disc.

PROGRESSION OF DISEASE AFTER 24 HOURS

In this group of monkeys the haemorrhages were extensive and darker and in all layers of the retina (Nos. 18, 21, 22, 23, 26, 28, 30, 33, 37, 38, 39, 40, 41, 44, 45). The amount and extent of retinal haemorrhages was a reliable indication of the presence of capillary nonperfusion. In some monkeys the haemorrhages were confluent, occupying the entire retina between the major blood vessels; in others the haemorrhages were arranged in a cluster fashion in the deep retina. Over the subsequent weeks there was gradual absorption of the haemorrhages, but intraretinal blood could be identified up to 8 weeks after occlusion.

In this group of monkeys the retinal vascular changes were characterised by capillary closure. In the most severely affected, closure was seen throughout the entire affected quadrant or hemisphere (Nos. 39, 41, 43, 44), while in others it was confined to the posterior pole or the peripheral retina (Fig. 6) (Nos. 40, 45). Closure was usually complete over large parts of the affected retina, and small patches of retinal nonperfusion within otherwise normally

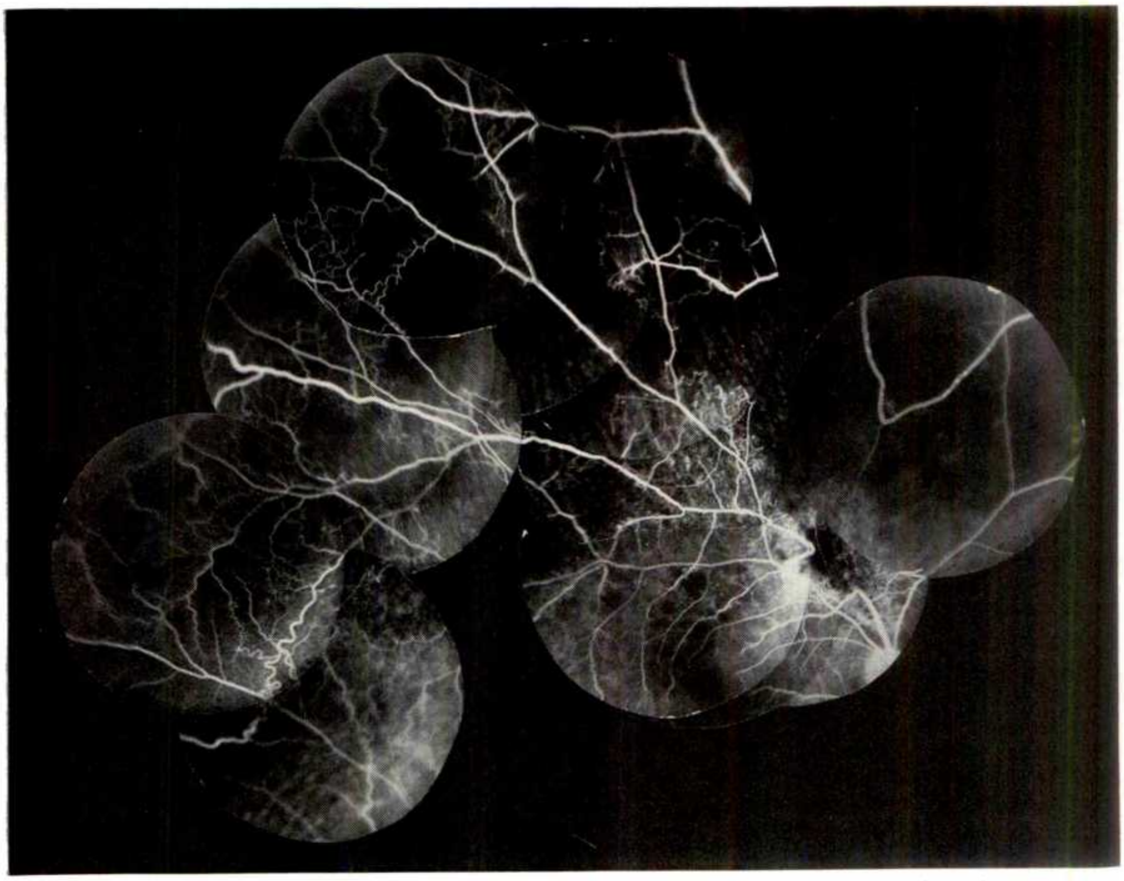


Fig. 6 *Composite photograph of a fluorescein angiogram showing extensive capillary closure involving the posterior pole and the peripheral retina*

perfused retina was seen rarely. Retinal capillary closure was identified as early as 5 hours (No. 14) and appeared to be a progressive phenomenon during the first 7 days following occlusion. After this period no increase of capillary closure was identified, but progressive changes occurred within the retina and major retinal vessels (No. 33).

Confluent closure of the peripheral capillaries was followed by nonperfusion of the major arteries and veins supplying that area (Fig. 7).

Closure of major retinal vessels was first identified 7 days after occlusion and was progressive over a subsequent period of 9 weeks. In 1 monkey slow perfusion in the quadrant was associated with an irregular calibre of venous lumen giving the appearance of 'beading' (No. 43). Major vessels crossing nonperfused retina showed accumulation of dye within the vessel wall during fluorescein angiography (No. 43), and these vessels subsequently became sheathed (Fig. 8) (Nos. 38, 39, 42); this change was limited to that length of vessel which crossed the ischaemic retina.

Within 28 days of the occlusion there was growth of vessels from the retinal veins into nonperfused retina (Fig. 9) (Nos. 41, 43, 44, 45). These 'intraretinal new vessels' first appeared as small outgrowths from the veins at right-angles to the main channel. Leakage was seen from the terminal ends of these growing vessels only (No. 44).

Revascularisation was seen in all monkeys with capillary nonperfusion. In most the revascularisation was extremely limited, while in others there was progressive growth of these vessels until the whole area of nonperfused retina became vascularised. During the period of growth there was constant remodelling of the capillary bed, and in 1 monkey closure of the newly formed vessels was observed (No. 44). All new vessels were within the neuroretina and did not grow through the internal limiting membrane.

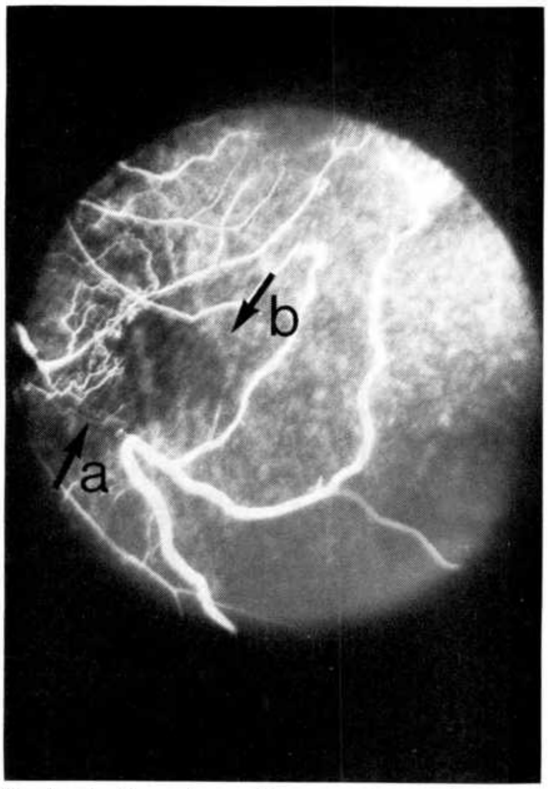


Fig. 7 *Capillary closure with a secondary venular (arrowed* a*) and arteriolar occlusion (arrowed* b*)*

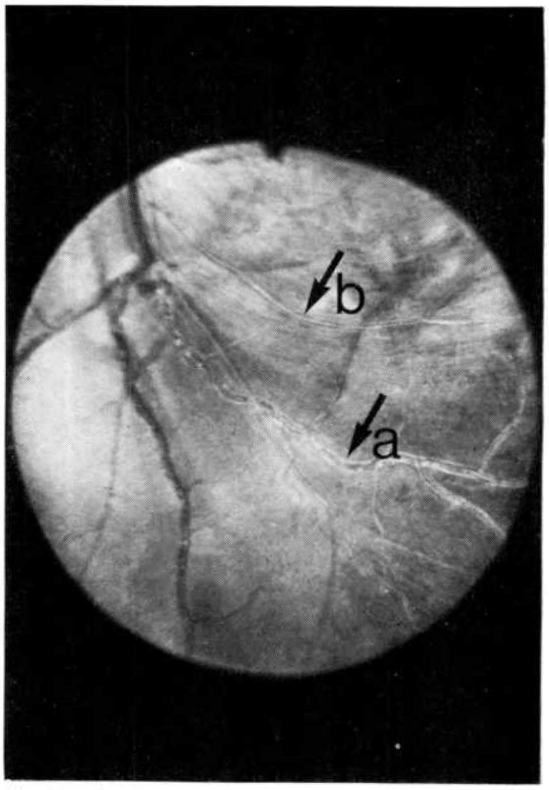


Fig. 8 *Black-and-white print of a colour photograph showing sheathing of retinal arteries and veins in the same area as Fig. 7. Retinal vein arrowed* a *and retinal artery arrowed* b

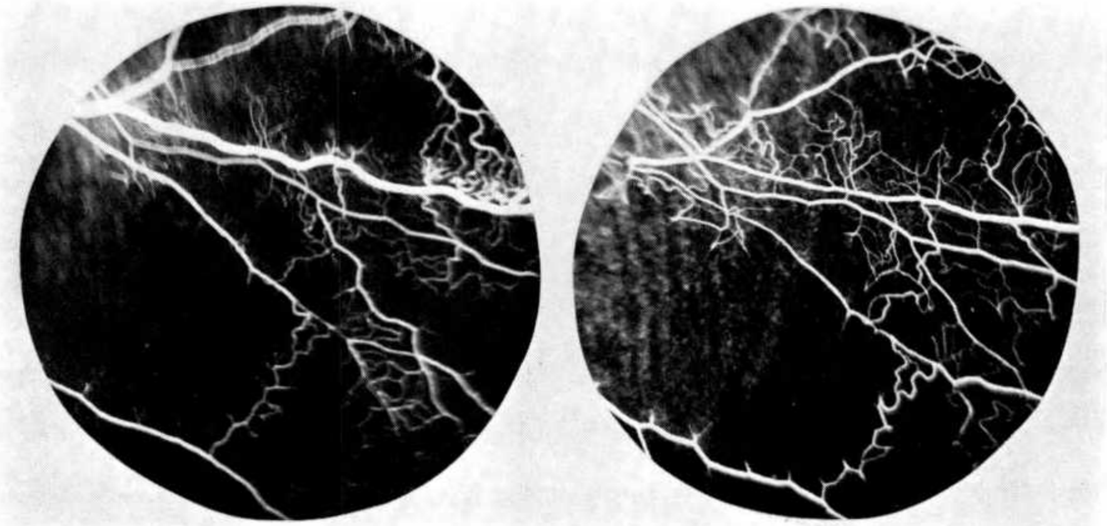


Fig. 9 *Fluorescein photograph 28 days after occlusion to show early growth of 'new vessels' into areas of capillary nonperfusion and subsequent appearance some 3 months later to show the progressive change*

There was progressive alteration in the appearance in the neuroretina over the subsequent weeks. At an early stage the retina was swollen, and in 4 monkeys multiple infarcts were seen (Nos. 18, 37, 39, 44). Within 4 weeks with absorption of the haemorrhages the retina became thin and atrophic, with loss of ganglion cell axons and segmented pallor of the optic disc, corresponding to the occluded quadrant or hemisphere.

In the monkeys that were observed for longer than 3 weeks there was progressive change within the pigment epithelium, with decrease in pigment content so that part of the fundus took on an orange colour. There was no pigment migration into the retina. Fluorescein angiography at no time showed evidence of any abnormality in the choroid except at the site of the laser occlusion.

Discussion

In order to study the pathogenesis of disease following venous obstruction experimental occlusion of retinal veins in animals has been undertaken by several workers. Becker and Post (1951), and Mutlu (1966) caused venous occlusion with the aid of transvitreal diathermy probes, and other workers used photocoagulation with xenon (Campbell, 1961; Linner, 1961; Okun and Collins, 1963; Voipio and Riatta, 1964; Kohner *et al.*, 1970; Archer *et al.*, 1974) or argon laser energy (Hamilton *et al.*, 1974; Coscas and Sterkers, 1977).

That permanent occlusion could be achieved in one session of photocoagulation in a majority of animals (34 of 45) differs from the experiences of Coscas and Sterkers (1977). It was certainly our impression that the presence of intravascular fluorescein aided occlusion, and this may account for the different observations. The closure rate was also better than that following xenon (Kohner *et al.*, 1970). Laser also had the advantage of the more accurate delivery system and small aperture, so that more precise lesions were created, and the arteries could be avoided more easily than with xenon.

The vein selected for occlusion was chosen well away from any adjacent arteries, so that the changes produced could be considered to be related to venous occlusion only. Inevitably some energy was absorbed within the choroid, but fluorescein angiography, both soon after occlusion and in the subsequent weeks, showed no apparent abnormality of the choroidal circulation. Delayed arrival of dye in the artery of the affected retina, slow capillary perfusion, capillary dilatation, and dye leakage were a constant feature in those monkeys examined within hours of occlusion. It was rare at this stage to see many retinal haemorrhages. These observations conform well with those in previous reports (Campbell, 1961; Okun and Collins, 1963; Kohner *et al.*, 1970; Archer *et al.*, 1976), and indicate that venous occlusion alone may produce the clinical appearance of 'acute retinal branch vein obstruction'. This conclusion is not new (Kohner *et al.*, 1970; Archer *et al.*, 1976; Coscas and Sterkers, 1977) but is at variance with the opinions expressed by Heyreh following his experimental (Heyreh, 1965) and clinical studies (Heyreh, 1971) of central vein obstruction. The circumstances which Heyreh has stated are necessary to produce the clinical appearance are high intraluminal pressure and ischaemia. Clearly both these are produced by venous occlusion due to the increased resistance to outflow, and arterial obstruction is not an essential prerequisite for such haemodynamic changes to occur. It might be argued that xenon photocoagulation is likely to cause coincident arterial lesions as was observed by Kohner *et al.* (1970) in some cases, but with the argon laser no arterial lesions could be detected clinically.

After the first 24 hours following venous occlusion the evolution of retinal disease fell into two distinct patterns. In the first, in which there was complete restoration of the retinal appearance and blood vessels to normal, relatively few haemorrhages were seen at 24 hours. By contrast in the second deep or cluster haemorrhages occurred throughout the affected retina, and these monkeys developed progressive capillary closure. That the subsequent evolution of change could be predicted accurately on the basis of the retinal appearance soon after venous occlusion corresponds precisely with human disease (Hamilton, 1976).

The presence of capillary closure as a late phenomenon was implied by the observations of Okun and Collins (1963), and Mutlu (1966). The latter reported that after the initial retinal changes two patterns of evolution could be seen. In some animals large collaterals formed between the affected part of the retina and its neighbours within 5 days, and the retina reverted to a normal appearance; in the others no collaterals were seen and progressive atrophy of the retina followed, with narrowing or closure of the large vessels and slow resorption of the haemorrhages. Kohner *et al.* (1970) studied in more detail the phenomenon of closure. Of the 11 pigs observed for more than 1 week there was closure in 1, and out of 8 monkeys there was closure in 5. However, in some of the animals the veins reopened after the initial closure and had to be reoccluded, and in several (3 of 5 monkeys with closure) the neighbouring artery was also closed. Failure to avoid the artery was probably related to the use of a xenon photocoagulator. Although they observed closure between 21 and 64 days after the initial occlusion, the relatively small number of observations make it impossible to identify the temporal profile of closure and those factors associated with this phenomenon. Curiously, Coscas and Sterkers (1977) failed to observe capillary closure despite using similar techniques. They considered that the closure was a late result of venous occlusion and that longer observation would have shown this change (Coscas and D'Hermy, 1978), but our results do not support this conclusion, since closure is an early change. Their failure to produce nonperfusion remains unexplained.

Our observations indicate that the process of closure took place during the 7 days after occlusion and rarely progressed beyond this time, and furthermore was usually complete over large areas of retina. Small areas of closure within otherwise normally perfused retina was unusual. It appears that capillary closure was a progressive and self-perpetuating phenomenon during the early and critical period of haemodynamic instability.

Kohner *et al* (1970) considered two possible factors which might influence capillary closure: firstly, that capillary endothelial damage due to a combination of high intraluminal pressure and ischaemia may induce intravascular thrombus formation; secondly, that the presence of tissue oedema may result in a rise in tissue pressure sufficient to cause capillary collapse. In addition, the rapid escape of plasma from the capillaries in the presence of slow flow may create intraluminal plugs of red cells and platelets (Hockley *et al.*, 1976), which would increase resistance to flow within the capillary bed and compound the ischaemia. It is difficult to judge the relative importance of these influences. The fact that capillary intraluminal pressure is raised and that capillaries do not reopen after resolution of retinal oedema argues against the concept that capillary collapse in response to raised tissue pressure is important. However, the presence of thrombi and cellular plugs within the vessels may reduce flow within the capillary bed and consequently reduce intraluminal pressure down stream from the obstruction. Moreover, widespread collapse would result in ischaemia and the consequent endothelial damage would mitigate against reopening of the vessel.

The presence of diffuse haemorrhage as a presage of closure may represent an indication of endothelial dysfunction whereby red cells are allowed to escape from the vessel lumen, and the presence of a static plug of erythrocytes within the capillary may also be important in the production of this phenomenon. That haemorrhage is common and widespread indicates that closure cannot be due to external pressure alone. It is possible that all three factors are relevant to the pathogenesis of capillary closure and that each may enhance the influence of the other.

If the cessation of flow and the height of intraluminal pressure were important in the production of closure, the rate of formation of efficient collateral channels would be critical, as has been suggested by Mutlu (1966). Because we undertook no formal measurement of the small collateral channels during the critical first week following venous obstruction it is possible that differences existed between the 2 groups of animals at this stage, but large collaterals were seen in animals of both groups 3 weeks or more after occlusion.

Changes in the major vessels occurred as a secondary phenomenon determined by capillary closure. Dye leakage occurred from both veins and arteries as they crossed areas of nonperfused retina and became sheathed during the subsequent weeks. This change in the major vessel wall appeared to be a response to local tissue ischaemia, since the major vessel appeared normal on either side of the ischaemic region. Progressive closure of the major vessels serving an area of nonperfused retina was also observed and took several weeks. That sheathing and closure of the major vessels followed some weeks after venous occlusion show that this change was purely a secondary phenomenon as it may be in man (Kohner and Shilling, 1976) and when observed after vein obstruction in man cannot be adduced as evidence of pre-existing arterial disease (Paton *et al.*, 1964).

New vessels arising at right-angles from retinal veins with leakage from the growing tip were seen consistently in monkeys with capillary nonperfusion and appear to be an attempt at retinal revascularisation. This appearance is identical to that described recently in human disease (Shilling and Kohner, 1976). In man these changes frequently precede the growth of vessels anterior to the limiting membrane, but in experimental animals this phenomenon was not observed.

Persistent oedema, which is a prominent cause of visual loss in human retinal vein occlusion did not occur; this accords with the observation of Coscas and Sterkers (1977).

Progressive atrophy of the inner retina can be accounted for by failure of retinal perfusion, but the retinal pigment epithelial changes are more difficult to explain. There was no evidence that choroidal perfusion was significantly altered, and it is unlikely that retinal vessel disease caused outer retinal ischaemia. Retinal haemorrhages were certainly extensive in these animals, and this may have influenced the outer retina and pigment epithelium, though progressive pigment epithelial changes were

Table 1 *Results of treatment*

Animal	*Treatment sessions*	*Duration of occlusion*	*Location of occlusion*	*Dose 85 Sr μC*	A/B × *100* (%)	A/C × *100* (%)
27	3	2 hours	ST	40	11·4	38·0
52	2	6 hours	SH	139	21·1	13·2
50	2	1 day	SH	250	35·1	30·8
32	1	3 days	ST	83	59·4	27·9
34	1	5 days	ST	98	2·3	1·2
35	1	5 days	ST	98	36·1	63·8
29	1	1 week	ST	60	29·9	19·3
30	1	1 week	SH	41·5	37·5	60·0
31*	1	1 week	ST	89	73·7	52·8
28	2	2 weeks	ST	58	100·0	91·5
Controls						
33	—	—	—	9·0	100·0	100·0
49	—	—	—	1201·0	120·1	91·5

A = 'Treated' area. *B* = Comparable area in opposite eye. *C* = Adjacent untreated inferior retina in treated eye.
ST = Superior temporal occlusion. SH = Superior hemisphere occlusion. *One hour's occlusion of superior temporal vein (untreated eye)

When these parameters were constant and normal, the left thorax was entered in the fifth intercostal space, the pericardium was incised, and a rapid injection of ^{85}Sr-tagged carbonised microspheres (obtained from Riker Laboratories, Loughborough, Leicestershire, 15±5 μm diameter, total dose 40 to 260 μCi) in a 2-ml agitated suspension was made into the left ventricle near its apex. Simultaneously arterial blood was withdrawn by an automatic infusion-withdrawal pump (Harvard Model 600–950 VDC) for 15 to 40 seconds from the femoral artery. The sample provided an arterial blood standard for radioactivity measurement as well as a means of calculating cardiac output. Immediately after the withdrawal of the arterial sample cardiac arrest was accomplished with rapid intravenous injection of potassium chloride.

PREPARATION OF EYES

For radioactivity counting. The eyes were enucleated and dissected in the coronal plane immediately posterior to the ciliary body. Hyaluronidase (1500 units) was injected into the posterior vitreous, to obtain easy separation of the ocular coats and vitreous. This was found to be unnecessary in the later experiments. The posterior ocular segments were orientated under a dissecting microscope, and radial cuts were made close to the vertical and horizontal meridians of sufficient length to allow the ocular coats to be flattened by pins to dental wax discs contained in Petri dishes or on to a moist pad of hardened filter paper (Whatman no. 50). Care was taken to avoid transecting larger retinal vessels. Discs of retina and choroid were incised together with a 5-mm diameter corneal trephine in the locations indicated in Fig. 1. The exact location varied from animal to animal depending on the distribution of the infarct. Particular efforts were made to excise tissue from corresponding locations of the 2 eyes of each animal. The discs of retina and choroid were removed from underlying sclera. The choroidal and retinal components were separated with care under microscopic magnification by means

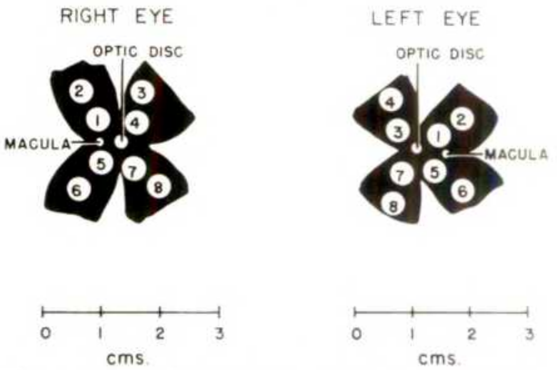


Fig. 1 *Pattern of dissection of retinae for radioactivity counting*

of a corneal spatula and sable brush. They were transferred on preweighed squares of lens paper to siliconised glass tubes for radioactivity counting. Choroid blood and radioactive standard samples were counted for 10 minutes and retinal discs for 30 minutes in a Wallac 80 000 automatic gamma counter.

The tissue samples were allowed to dry to constant weight for a minimim of 24 hours and were weighed on a Cahn Electrobalance (Model G).

After subtraction of the background radioactivity tissue radioactivity was calculated as counts per minute per milligramme of dry weight. Retinal counts only will be reported in this paper.

For autoradiography. Radial cuts were made similar to those above, before the retinae were separated from their respective choroids with sable brushes. The isolated retinae were then flattened on large microscope slides (50 × 76 mm) and overlayed with a portion of a second microscope slide. The resultant slide-tissue matrix was placed in an empty Petri dish, which was slowly filled with a fixative solution composed of 2·5% gluteraldehyde buffered in 0·1 M sodium cacodylate containing 10 mg/ml calcium chloride with a final pH of 7·4. After several minutes the upper slide was carefully oscillated to allow penetration of the fixative but with care to prevent deformation of the retina.

After overnight fixation preparations were washed in a sucrose buffer and mounted flat on clean glass slides smeared with egg albumen. The preparations were air-dried for 2 days before being transferred to a dark room, where they were placed tissue side down on sheets of Structrix 7 (Agfa) *x*-ray film. The slides were stabilised with small brass weights and the orientation recorded by marks placed on the film around the edges of the slide. The preparations were stored in a light-tight box at 4°C for 3 days. After this the film was carefully separated from the retina and developed in D17 (Kodak) for 5 minutes before being fixed in Kodak acid fixing powder.

The developed autoradiographs were orientated over their initiating tissue samples by the marks made on the film, and the retinal boundaries and topography were traced on to the autoradiograph in ink (Figs. 2, 3, 4).

Results

Two control animals were studied after injection of radioactive microspheres. Matching areas of the retinae of their left and right eyes were excised. The ratio of counts in these areas was 1·00 in monkey no. 33 and 0·91 in monkey no. 49. This indicates uniform entry of microspheres into undamaged retinal tissue of the 2 eyes.

The results in the 10 experimental animals studied by radioative counting are given in Table 1. The mean ratio of counts in the area of the occluded vein compared with the matching area in the opposite retina was 0·41. When compared with the adjacent inferior retina of the same eye the ratio was 0·40.

A comparison was also made between the matching control area in the opposite retina and the adjacent control area. The matching: adjacent ratio averaged 1:16. This finding is of interest as it confirms the reproducibility of the measurements for similar treated areas, and it indicates that there was no compensatory increase of flow through the adjacent retinal area as a consequence of the vein occlusion.

The anomalous result in monkey no. 28 which had no reduction of blood flow at the time of measurement 2 weeks after occlusion may be explained by the development of a profuse collateral supply. This was noted on the fluorescein angiograms.

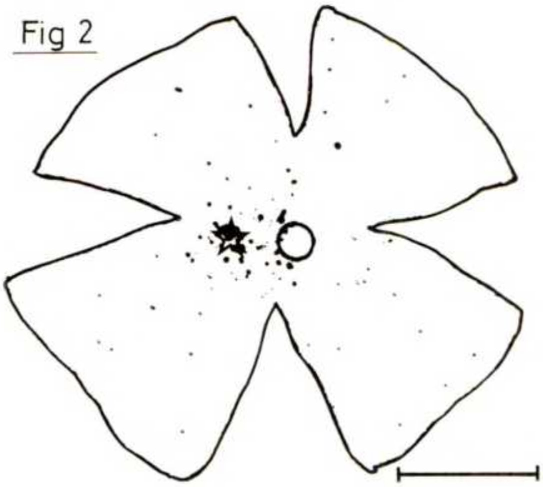
The reduction of radioactivity was similar in eyes which had superior temporal and superior hemisphere branch vein occlusions, and the extent of reduction was independent of the duration of the occlusion. A considerable reduction of flow was evident at the earliest times of measurement after vein occlusion, 2 and 6 hours. The reduction of flow in the group was highly significant ($P<0·01$).

Five eyes were studied by autoradiography. Two were control retinae which showed an even distribution of flow, apart from the macular area, in which there was a greater number of microspheres (Fig. 2). The 2 animals with vein occlusions both had obstructed hemisphere veins, one of 5 days' and the other of 1 week's duration. In one (5 days) there was very little penetration of spheres into the occluded area and in the other (1 week) markedly less than comparable areas of the normal retina (Figs. 3, 4).

Discussion

We have demonstrated that between the durations of 2 hours and 1 week laser-induced retinal branch vein occlusion in the monkey leads to markedly reduced entry of tagged microspheres into the affected region. This indicates a reduction of blood flow. We chose microspheres with a diameter of 15 ± 5 μm in the expectation that the spheres would become impacted in capillaries and precapillary arterioles. Our earlier experience with the experimental vein occlusion model indicates that, as judged by fluorescein angiography and morphological studies, capillary closure only rarely occurs earlier than 24 to 48 hours (Hockley *et al.*, 1979). Fluorescein studies, however, show an early delay of arterial

Fig 2



Figs. 2, 3, 4 *Autoradiographs of isolated monkey retinae after intracardiac injection of radioactively labelled microspheres. The position of the optic disc is indicated by an open circle and that of the macula by a star. Bar = 1 cm.* (2) *Autoradiograph of an untreated retina showing a relatively uniform distribution of label but with a concentrate around the macula.* (3) *Autoradiograph of a retina in which a superior hemisphere vein has been obstructed for 5 days. Note the reduction of the label in the superior temporal quadrant of the retina.* (4) *Autoradiograph of a retina in which a superior hemisphere vein had been occluded for 7 days. In this sample the reduction of label is most marked in the superior nasal quadrant*

Fig 3

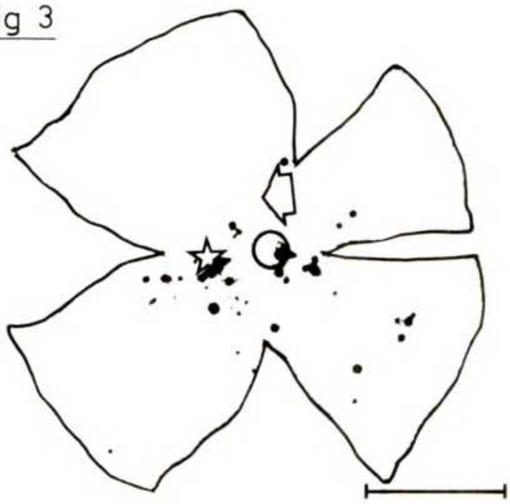
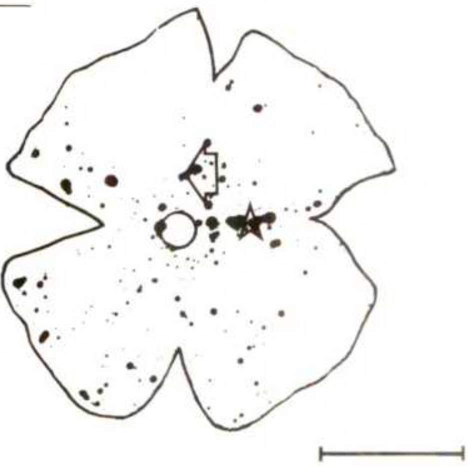


Fig 4



perfusion of the affected area (Hamilton *et al.*, 1979).

The reduced radioactivity as early as 2 hours in the counting experiments and 5 hours in the autoradiographic studies was therefore an interesting finding. Its origin is, however, unclear. Collapse of the retinal capillaries due to pressure by oedema was not found, nor could transmural pressure be sufficiently high. The most likely explanation is back pressure from the veins in which blood is stagnating at a time when collaterals of adequate diameter had no time to develop.

The results presented in Table 1 illustrate some of the difficulties of applying the microsphere method to small portions of tissue with a relatively poor blood supply such as the retina. Study of the radioautographs indicates that the number of microspheres lodged in a 5-mm diameter disc of retina might be small, and thus the statistics of counting would be poor. However, this would not explain the large differences between animals in the number of spheres entering similar areas of the retina. The explanation of this variability must lie in either uneven mixing of the microspheres in the flowing blood or highly variable retinal perfusion. As care was taken to study animals only when the blood gases and the blood pressure were stable, the former explanation seems more likely.

The relative sparsity of microspheres and the unevenness of their distribution also gave rise to difficulties in interpretation of the autoradiographic preparations. The differences in size and density of the photographic images suggest that it is not rare for more than one sphere to be lodged in a single minute vessel. Most probably this was the result of the flow pattern and the anatomy of the retinal circulation. In previous studies with glass spheres we have noted a tendency for the spheres to go repeatedly to the same vessel or area of the retina (Dollery *et al.*, 1965). None the less, both the studies with the radioactive counting and the autoradiographic studies were in agreement as to the magnitude and the distribution of blood flow reduction.

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seen in areas without macroscopic haemorrhage and progressed for a long time after intraretinal blood had disappeared.

Retinal vein occlusion in rhesus monkeys produces acute changes which simulate precisely those in man, and the evolution of the disease is similar to that seen in many patients. However, it was disappointing that persistent oedema and preretinal neovascularisation, which are the two major sight-threatening complications of venous occlusion in man, did not appear. These obvious differences may be due to differences between the circumstances of spontaneously occurring venous occlusion in man and the experimental homologue in primates. In man the problem arises in patients with coexistent vascular disease (Kohner *et al.*, 1975) as opposed to the young healthy monkeys. The behaviour of blood vessels is certainly modified by age and by vascular disease. It should be emphasised that spontaneous retinal venous occlusion has not yet been achieved in experimental animals by manipulating systemic dysfunction.

This study was generously supported by the Wellcome Trust.

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Experimental retinal branch vein occlusion in rhesus monkeys. II. Retinal blood flow studies

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SUMMARY Experimental branch vein occlusion by laser photocoagulation in the rhesus monkey leads to early, marked, and lasting reduction of blood flow to the affected retinal region. The radioactive microsphere method demonstrates this reduction of blood flow in both gamma counting and autoradiography. The reduction of flow becomes evident as early as 2 hours after occlusion and persists up to 1 week. The mechanism of the altered flow is discussed.

The clinical features of retinal branch vein occlusion are well established both in man (Raitta *et al.*, 1971) and in experimental animals (Hayreh, 1965; Fujino *et al.*, 1968; Kohner *et al.*, 1970; Hamilton *et al.*, 1974). Considerable doubt remains concerning the role of arterial disease and perfusion of the affected retina in the pathogenesis of the disorder. In particular it is not known what the cause of capillary nonperfusion is, nor is it known how blood flow is changed in the immediate and early days following occlusion.

Clinical methods for the measurement of retinal blood flow in man are not available at the present time. In experimental animals the intracardiac injection of radioactively (strontium-85) tagged microspheres (15±5 μm) give a reliable measure of regional blood flow (Hoffbrand and Forsyth, 1969). We employed a modification of this method (Alm and Bill, 1972, 1973) in an attempt to assess changes in retinal blood flow following experimental occlusion of retinal veins in the rhesus monkey.

Methods

PREPARATION OF ANIMALS

Rhesus monkeys weighing 3 to 5 kg were anaesthetised as described in the previous paper (Hamilton *et al.*, 1979). Retinal colour photographs and fluorescein angiography (intravenous 10% sodium fluorescein) facilitated the selection of veins for occlusion. In all instances the venous segment occluded was within 1 disc diameter of the disc but sufficiently removed from an associated arteriole to avoid the possibility of damaging the arteriole during the occlusion. Variation between individual animals led to the production of superior temporal branch vein occlusion in some animals and superior hemisphere vein occlusion in others (Table 1). One eye, the left, was treated, while the right served as an untreated control. In 1 animal (31) the superior temporal veins in both eyes were occluded. In this animal the right eye was occluded 1 hour before injection of microspheres. Two animals (Nos. 33 and 49) were left untreated in order to assess eye-to-eye and segment-to-segment variation.

Occlusion was achieved by using an argon laser (Coherent Radiation Model 800) with a 50-μm spot size, an exposure time of 0·2 seconds, and energy levels of 100 to 250 mW. Repeated applications were made until the treated segment of vein appeared occluded on ophthalmoscopic examination. The occlusion was confirmed by fluorescein angiography carried out ½ to 1 hour after coagulation. If subsequent examination, after hours or days, revealed resumption of blood flow, the initially treated segment was again coagulated. Most veins remained occluded after a single treatment; in some up to 3 sessions of treatment were necessary (Table 1). The length of follow-up was calculated from the time a permanent occlusion was achieved.

On the day of enucleation colour photography and fluorescein angiography were performed on both eyes in each animal. Femoral artery catheters were introduced into both legs to permit monitoring of pH, P_{O_2} and P_{CO_2} and blood pressure and to allow the measured withdrawal of arterial blood.

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Experimental retinal branch vein occlusion in rhesus monkeys. III. Histopathological and electron microscopical studies

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SUMMARY Experimental retinal vein occlusion in monkeys was followed by an immediate increase in capillary permeability which was accompanied by retinal oedema. This functional capillary change was followed at about 6 hours after occlusion by structural damage to the capillary wall. Thrombus formation occurred in the damaged vessels, and areas of stasis were thus produced with associated retinal haemorrhages. Finally, there was complete loss of the capillary endothelium and pericytes, and the acellular capillaries were invaded by proliferating glial cell processes, so producing permanent capillary closure.

The clinical and fluorescein angiographic picture of experimental retinal branch vein occlusion in monkeys has been described in the preceding communication (Hamilton, *et al.*, 1979). Selected retinae of some of the same monkeys have also been examined histologically and by electron microscopy, and in this communication we present the corresponding microscopical observations on the early stages and progression of the disease. In particular, observations have been made on the alterations which occur in the capillaries as a result of vein occlusion. Thus histological and ultrastructural explanations are provided for the clinical condition of delayed perfusion and a sequence of changes leading to irreversible capillary closure is described.

Materials and methods

Branch or hemisphere retinal veins of adult rhesus monkeys were occluded with an argon laser at a site close to the optic disc. Details of the technique have been described in the preceding communication (Hamilton *et al.*, 1979). In nonsurvival experiments both eyes of a monkey were utilised and the animal was kept under anaesthesia for the whole period of the acute occlusion in the second eye. The eyes were enucleated from anaesthetised monkeys at the end of the selected duration of occlusion (Table 1).

HISTOLOGY AND ELECTRON MICROSCOPY

Immediately after enucleation a small cut was made with a razor blade at the ora serrata of the eye. The cut was enlarged with scissors to about a quarter of the eye's circumference and the eye was quickly placed in fixative. Most of the eyes were fixed initially in 3% glutaraldehyde in 0·1 M sodium cacodylate buffer pH 7·4, containing 1 mg/ml of calcium chloride. The eyes were fixed for 18 hours in glutaraldehyde; fixation commenced at room temperature but continued at 4°C after a few hours. At the end of fixation the anterior segment was removed completely and the retina and posterior part of the eye were rinsed in cacodylate buffer containing calcium chloride and 75 mg/ml of sucrose. At this stage the fundus was examined macroscopically in conjunction with fluorescein angiographs, and pieces of the retina and choroid approximately 2×4 mm in size were removed for further processing.

The pieces of retina, which usually displayed vascular leakage or capillary closure, were taken mainly from the area between the site of occlusion and the macula and from the area temporal to the macula; a few specimens were taken from an area nasal to the occlusion. A control, unaffected part of the retina was selected from the opposite side of the macula to the occlusion. The actual site of the occlusion was examined in some eyes (Nos. 2, 7, 11, 15, 16, and 22).

The specimens were postfixed for 3 hours at 4°C in 1% osmium tetroxide in either 0·14 M veronal acetate buffer or 0·1 M s-collidine buffer, pH 7·4. Specimens from a few monkeys were fixed only in osmium tetroxide (Table 1) and some of the specimens received a final fixation of 1·5 hours at 4°C in an 0·5% aqueous solution of uranyl acetate

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Table 1 *Monkey retinae examined by light and electron microscopy after retinal branch vein occlusion*

*Eye number**	*Occluded vein*	*Duration of occlusion*	*Summary of clinical and macroscopical observations*	*Vascular perfusion tracers*	*Fixation*
1	Right superior temporal branch	1 h 15 min	Slight oedema. Deep haemorrhages	—	GA OsO_4 FS for digest
2	Left superior hemisphere	1 h 30 min	Pronounced oedema. Dilatation of capillaries and terminal venules with leakage. Small haemorrhages superior to macula. No closure	Peroxidase	GA OsO_4
3	Right inferior hemisphere	2 h	Pronounced oedema. Dilatation of capillaries and terminal venules with leakage. No haemorrhages. Delayed filling of affected retina. Early capillary collaterals temporal to macula	—	OsO_4 FS for digest
6	Right inferior hemisphere	2 h	Pronounced oedema. Dilatation of capillaries and terminal venules with leakage. Few small superficial haemorrhages. No closure	Colloidal carbon	FS for digest
7	Right inferior hemisphere	2 h 30 min	Pronounced oedema. Dilatation of capillaries and terminal venules with leakage. No haemorrhages. No closure	Colloidal iron and colloidal carbon	GA OsO_4 UA
11	Left inferior hemisphere	3 h 30 min	Some oedema. No fluorescein photographs	Peroxidase	GA OsO_4
13	Left inferior hemisphere	4 h	Some oedema. Small haemorrhages inferior to macula. No fluorescein photographs	Peroxidase	GA OsO_4
14	Right inferior hemisphere	5 h 30 min	Some oedema. Dilatation of capillaries and terminal venules with extensive leakage. Few superficial haemorrhages. Delayed filling of affected retina. Small area of capillary nonperfusion	—	GA OsO_4 UA
15	Right superior hemisphere	7 h	Some oedema. Few superficial haemorrhages. No fluorescein photographs	Colloidal iron	GA OsO_4 UA
16	Left inferior hemisphere	24 h	Some oedema. Dilatation of capillaries and terminal venules with leakage. Few scattered haemorrhages. Some small areas of capillary nonperfusion	—	OsO_4 FS for digest
22	Left inferior hemisphere	7 days	Some oedema. Dilatation of capillaries and terminal venules with leakage. Extensive haemorrhages. Capillary closure	Colloidal iron and colloidal carbon	GA OsO_4 UA
32	Left inferior hemisphere	14 days	No oedema. Capillary and terminal venular leakage. Extensive haemorrhages and cotton-wool spots adjacent to occlusion. Large areas of peripheral capillary nonperfusion	Colloidal carbon	FS for digest
33	Right inferior hemisphere	14 days	No oedema. Extensive deep haemorrhages. Capillary nonperfusion. Veins appear as white lines. Large collaterals temporal to macula	Peroxidase	GA OsO_4 UA
41	Left inferior hemisphere	35 days	No oedema. Haemorrhages. Capillary closure. Venous and arterial narrowing and sheathing	—	OsO_4 FS for digest

*Eye numbers are the same as those used in preceding communication. GA = Glutaraldehyde. OsO_4 = Osmium tetroxide. UA = Uranyl acetate. FS = Formol saline

adjusted to pH 5 and containing 45 mg/ml of sucrose (Table 1). All specimens were dehydrated in ethanol and embedded in Araldite. Thick and thin sections were cut with glass knives and a LKB ultramicrotome. Thick sections were stained with toluidine blue for light microscopy; thin sections were stained with alcoholic uranyl acetate and lead citrate and examined with a JEM 100C electron microscope.

TRACER PERFUSION

The retinal blood vessels of some eyes were examined by light microscopy after perfusion of the monkeys with *(a)* colloidal carbon or by electron microscopy after perfusion with *(b)* colloidal iron, or *(c)* horseradish peroxidase (Table 1).

(a) Approximately 100 ml of colloidal carbon (Indian ink: Kandadar) was injected through a wide-bore needle into the left ventricle of the heart

5 minutes before the eye was enucleated. The eye was fixed in formol saline and the retina was examined first as a flat preparation and subsequently as a digest preparation. The retina was separated from the choroid before it was mounted, and the pigment epithelium was removed by gentle brushing. The choroid of 1 eye (No. 6) was also examined as a flat preparation.

(b) 5 ml of saccharated colloidal iron (Evans), equivalent to 100 mg iron, was injected into the carotid artery 5 minutes before the eye was enucleated and processed in the normal way for electron microscopy.

(c) 1 g of crude horseradish peroxidase (Sigma) in 5 ml of saline was injected into the femoral vein 15 minutes before the eye was enucleated. After glutaraldehyde fixation the specimens were cut into slices approximately 100 μm in thickness and incubated in 3·3′-diaminobenzidine tetrahydrochloride according to the method of Graham and Karnovsky (1966). The specimens were then treated according to the normal schedule but without uranyl acetate fixation.

DIGEST PREPARATIONS

Retinae or parts of retinae of some monkeys (Table 1) were digested by the technique of Ashton (1963). The preparations were stained with haematoxylin and eosin.

Results

The observations on individual eyes are grouped into 3 postocclusion time periods: 1 to 4 hours, 5 to 24 hours, and 7 to 35 days. For each of these periods 3 aspects of the eye are described: *(a)* the appearance of the vein and adjacent retina and choroid at the site of occlusion; *(b)* the changes in the retinal microvasculature in the territory of the occluded vein; *(c)* changes in the nonvascular or neural cells of the retina and associated tissues, again in the area drained by the occluded vein.

1 TO 4 HOURS AFTER OCCLUSION

(a) *Site of occlusion (eyes 2, 7, 11)*

Examination of the actual site of the laser burn revealed that the occluded vein was filled with erythrocytes, platelets, and fibrin. The vessel was distended by its contents and the endothelium was totally degenerate and absent in many places. The muscle cells of the vessel wall were also necrotic but the basement membranes were present so that there were no complete breaks or gaps in the wall. The inner retinal layers were highly degenerate within a distance of approximately 500 μm (0·5 mm) from the vein, and the outer layers and choriocapillaries were damaged over a slightly greater area. However, beyond a distance of approximately 1 mm from the vein occlusion the retina appeared to be normal. The neighbouring artery also appeared to be undamaged by the vein occlusion.

(b) *Retinal vascular changes (eyes 1, 2, 3, 6, 7, 11, 13)*

Many of the capillaries in the territory of the occluded vein appeared to be completely normal at these early times and no abnormalities were detected in digest preparations. A flat preparation of the retina from the eye (No. 6) which had been perfused with carbon showed engorgement of the occluded vein, and there was also more prominent filling of the obstructed parts of the capillary bed than in the unaffected areas.

Sections of dilated venules showed their thin or flattened endothelial cells with spindle-shaped nuclei. No damage or breaks in the endothelium were detected, and apart from the change in shape the cells appeared normal. Dilated capillaries with a wide lumen and a thin endothelium (Fig. 1) were present in the sections, but the same specimens also contained capillaries with a shrunken or compressed appearance (Fig. 2). The latter vessels were often adjacent to small areas of severe retinal oedema. The cross-sectional shape of the flattened vessels was irregular and the endothelial cell nuclei were indented and folded, but the most abnormal feature was the slit-like state of the lumen (Fig. 2). The cytoplasm of the endothelium was slightly more electron-dense than normal, and at later times the mitochondria were swollen. Similar, and occasionally more marked cytoplasmic changes were seen in the pericytes.

Although no morphological site of leakage was identified, all the specimens had a few erythrocytes outside the blood vessels. The extravascular blood cells were situated between the neural cells, and they were adjacent to capillaries which were entirely normal. The flat preparation of carbon perfused vessels revealed one small area of carbon leakage in the obstructed microvasculature temporal to the macula. Leakage was best demonstrated in a specimen (No. 2) perfused with peroxidase. The electron-dense peroxidase reaction product was visible in the lumens of all the capillaries (Fig. 3*a*), including those with a slit-like lumen. Peroxidase was also found in small extracellular spaces adjacent to some capillaries and larger amounts of extracellular peroxidase were present in the outer plexiform layer (Fig. 3*a*). The basement membrane of the capillaries often contained peroxidase, and there were vacuoles and smaller pinocytotic vesicles containing peroxidase in the endothelial cells. These vesicles were seen opening both to the lumen and to the basement

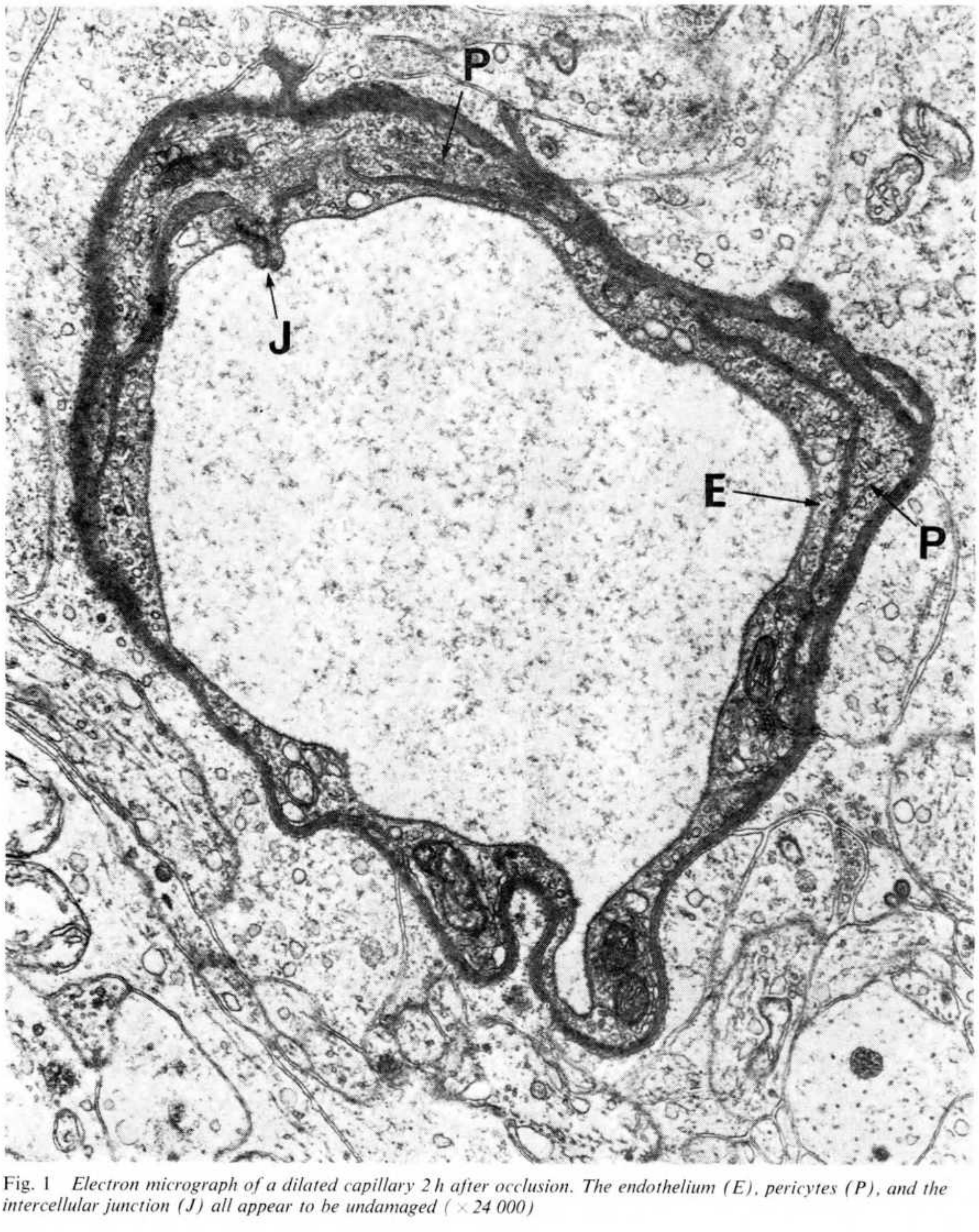


Fig. 1 *Electron micrograph of a dilated capillary 2 h after occlusion. The endothelium (E), pericytes (P), and the intercellular junction (J) all appear to be undamaged (× 24 000)*

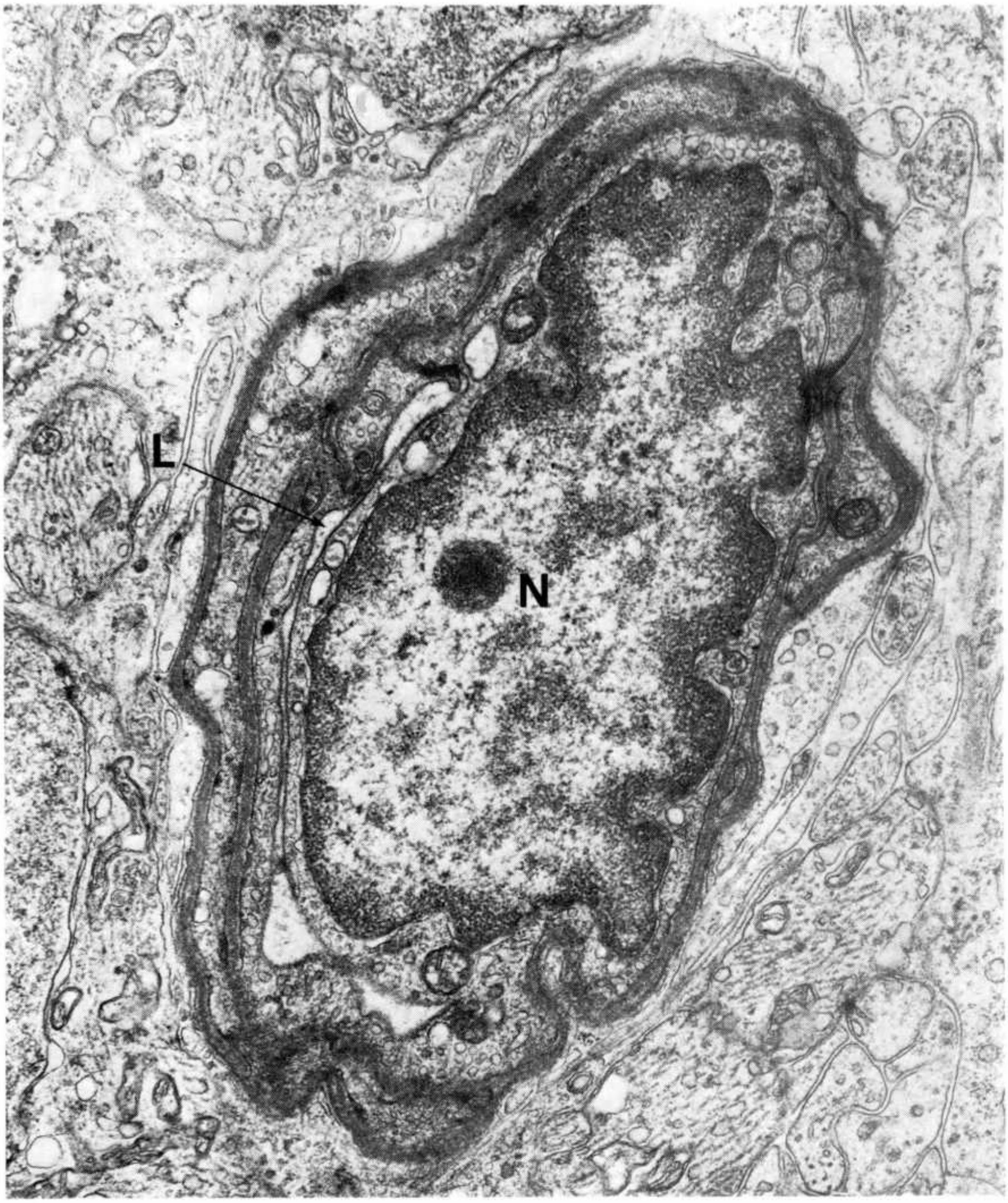
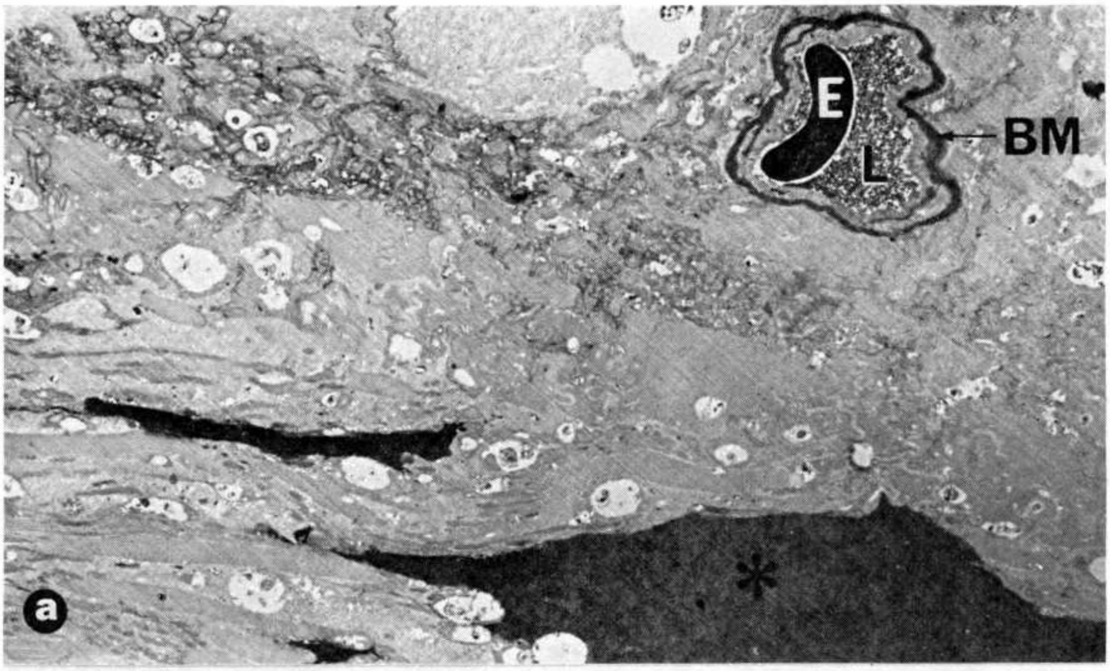


Fig. 2 *Capillary with a thin and flattened lumen (L) 2 h after occulsion. The endothelial nucleus (N) has an irregular and indented outline but otherwise the cells appear to be normal. Electron micrograph (× 24 000)*



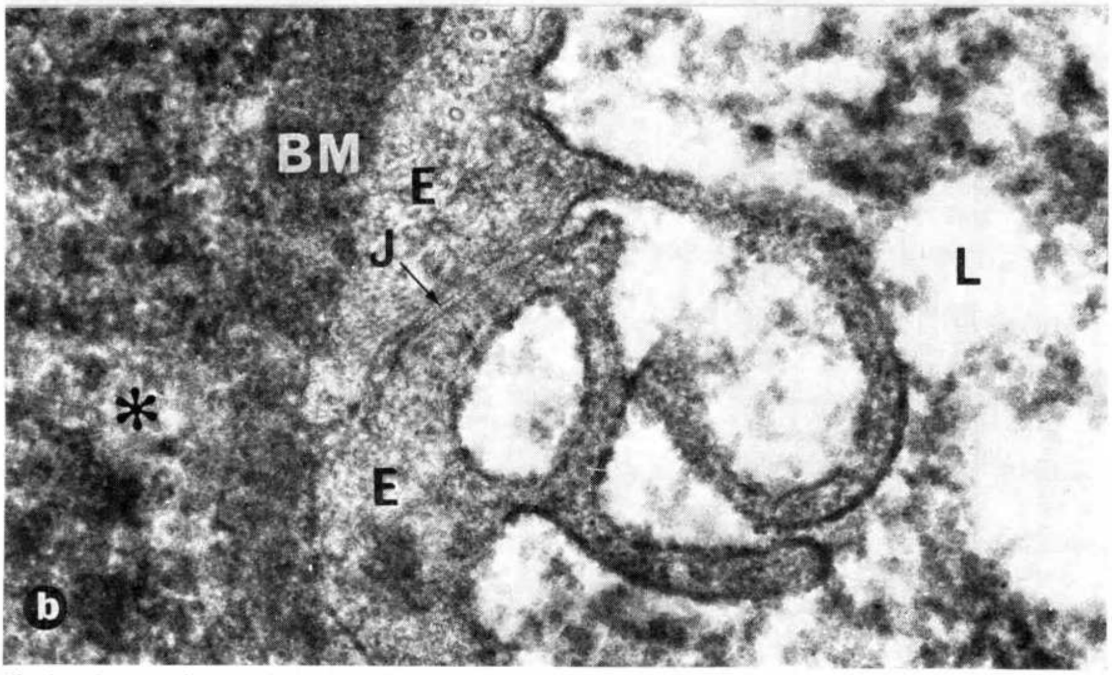


Fig. 3a *Section of retina which was perfused with horseradish peroxidase at 1·5 h after occlusion. The dense precipitate of peroxidase reaction product is visible in the capillary lumen (L) together with an erythrocyte (E). Peroxidase is also present in the basement membranes (BM) and there are large deposits* (*) *in the outer plexiform layer. Electron micrograph (× 3800)*

Fig. 3b *Junction (J) between 2 capillary endothelial cells (E). Dense peroxidase granules are present in the capillary lumen (L) and in the basement membrane (BM), and there is a large extravascular accumulation of the enzyme* (*), *but the dense precipitate is not seen in the junction. 1·5 h after occlusion. Electron micrograph (× 84 000)*

membrane. Numerous endothelial junctions were observed with peroxidase in the adjacent lumen and in the adjoining basement membrane, but there was no evidence that peroxidase passed through the junction (Fig. 3*b*).

(c) *Other retinal changes (eyes 1, 2, 3, 7, 11, 13)*
The most prominent early change in the nonvascular tissues of the retina was intracellular oedema. At the earliest times after occlusion the nerve fibres and mitochondria in the inner layers were swollen, and later the vacuolation was more extensive, with small areas of extracellular oedema and some pyknotic nuclei. In the most severely affected specimens the oedema could be observed macroscopically in the macular region; the inner layers were completely disorganised, and there was gross swelling with accumulations of exudate in the plexiform layers. The vacuolation was generally less marked in the nerve fibre layer close to arterioles. Conversely, pronounced vacuolation occurred in the plexiform layer adjacent to venules. The outer nuclear layer and the rods and cones always remained undamaged, and control specimens from an area of retina not drained by the occluded vein displayed markedly less vacuolation than was found in the territory of the occlusion.

5 TO 24 HOURS AFTER OCCLUSION

(a) *Site of occlusion (eyes 15, 16)*
The occluded vein retained the same appearance as at earlier times with severe oedema and haemorrhages in the adjacent retina. A small area of the nerve fibre layer in 1 specimen (No. 6) had grossly swollen axons which were filled with numerous dense bodies. In the same specimen (No. 6) a few of the larger choroidal vessels were completely filled with lysed erthrocytes, leucocytes, platelets, and fibrin.

(b) *Retinal vascular changes (eyes 14, 15, 16)*
These specimens showed a range of degenerative changes in the capillaries, including the slit-like lumen, vacuolation, and mitochondrial swelling. A more consistent feature of the capillaries was the presence of erythrocytes that had moved out of the capillary lumen and were lodged beneath the endothelial basement membrane (Fig. 4). Most of these intramural red cells appeared normal, but some were obviously lysed. A few white blood cells were seen migrating out from a venule, and some fibrin was also found in the walls of capillaries. Although the intramural red blood cells were outside the pericyte plasma membrane, the adjacent pericyte cytoplasm was vacuolated and the nucleus was dense and granular and appeared to be shrunken (Fig. 4). In many instances the endothelium appeared undamaged in comparison to the pericytes, and it showed no sign of the previous passage of an erythrocyte through or between the cells (Fig. 4).

Another characteristic change in some of the capillaries at later times was engorgement of the lumen with erythrocytes or, occasionally, platelets. These vessels usually had a thin, electron-dense endothelium, but the platelets were associated with more severe degenerative changes including small endothelial breaks (Fig. 5). Electron-dense plasma, fibrin, and leucocytes were often present with the platelets, and a few capillaries were found that were completely blocked with a thrombus of fibrin and plasma (Fig. 6). The endothelium and pericytes of these vessels were totally necrotic and absent in some areas, so exposing the basement membranes (Fig. 6).

Colloidal iron was visible in minute amounts in the lumen of some normal capillaries, but larger amounts of the dense precipitate were seen in capillaries filled with platelets. The tracer appeared to be trapped between the platelets and was also closely associated with fibrin. Colloidal iron was never observed in the wall of the capillary or outside the vessel.

A digest preparation of the retina with the 24 hour occlusion did not reveal any abnormality apart from some degeneration of the peripheral capillaries.

(c) *Other retinal changes (eyes 14, 15, 16)*
These monkeys were the first in the time series to have macroscopically visible retinal haemorrhages. At 7 hours small, diffuse, and flame-shaped haemorrhages were scattered throughout the occluded half of the retina. Sections showed that the extravascular red blood cells were almost entirely confined to the nerve fibre and ganglion cell layers. The severe oedema seen at earlier time was also present, particularly in the nerve fibre layer and in the outer plexiform layer of the macular region.

The 24-hour specimen had a large intraretinal haemorrhage which extended from the site of occlusion to the macula. The retina was swollen to 2 or 3 times its normal thickness by the large accumulation of erythrocytes in the nerve fibre and outer plexiform layers. Sections taken at the edge of the large haemorrhage revealed small numbers of erythroyctes in all retinal layers. There was also extensive oedema and some pyknotic nuclei in the outer nuclear layer.

7 TO 35 DAYS AFTER OCCLUSION

(a) *Site of occlusion (eye 22)*
At 7 days the occluded vein and its larger branches were filled with cell debris, platelets, and fibrin even

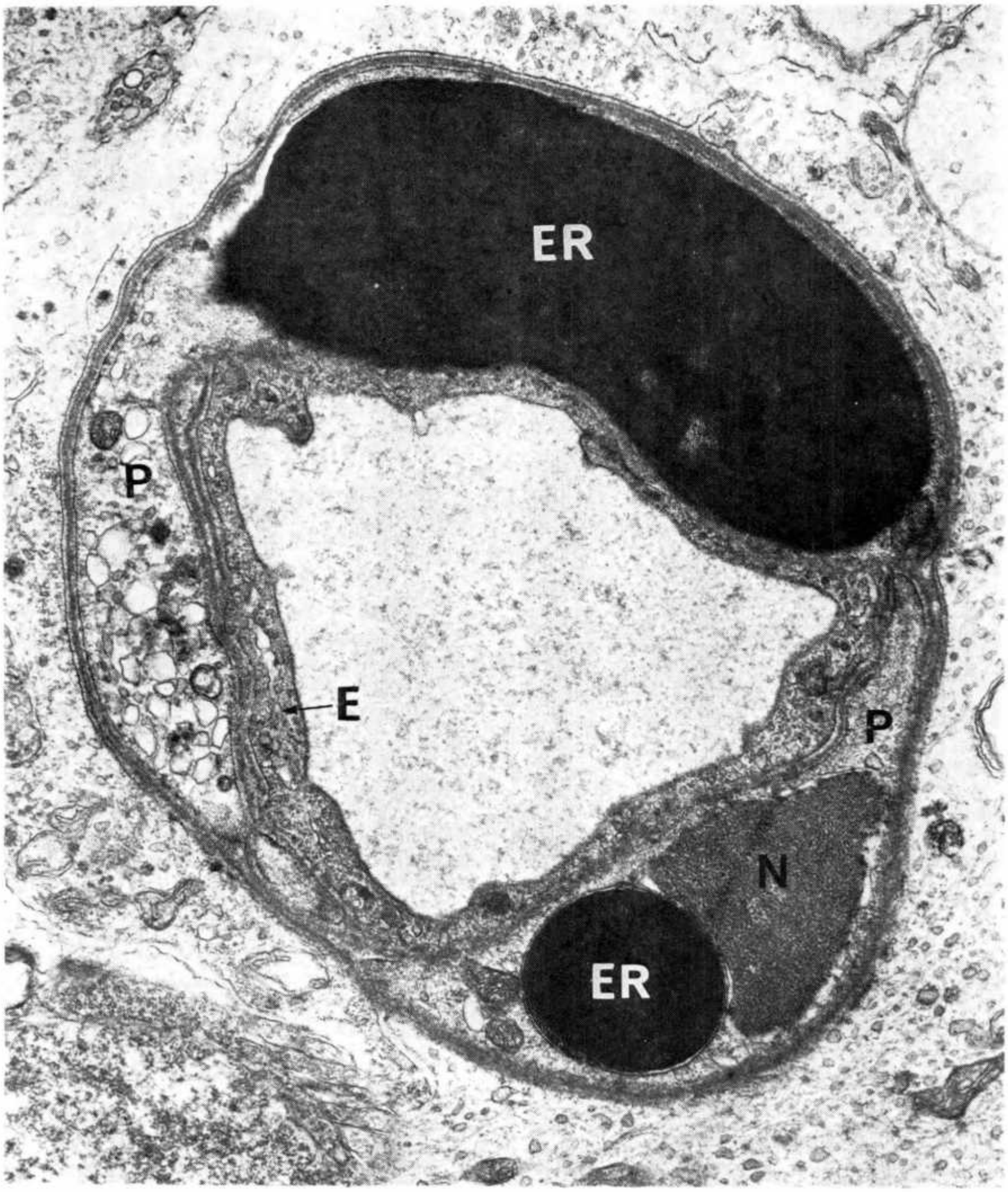


Fig. 4 *Erythrocytes (ER) in the wall of a capillary. The adjacent pericyte (P) is vacuolated and the pericyte nucleus (N) is dense and granular. The endothelium (E) appears to be undamaged. 24 h after occlusion. Electron micrograph (× 20 000)*

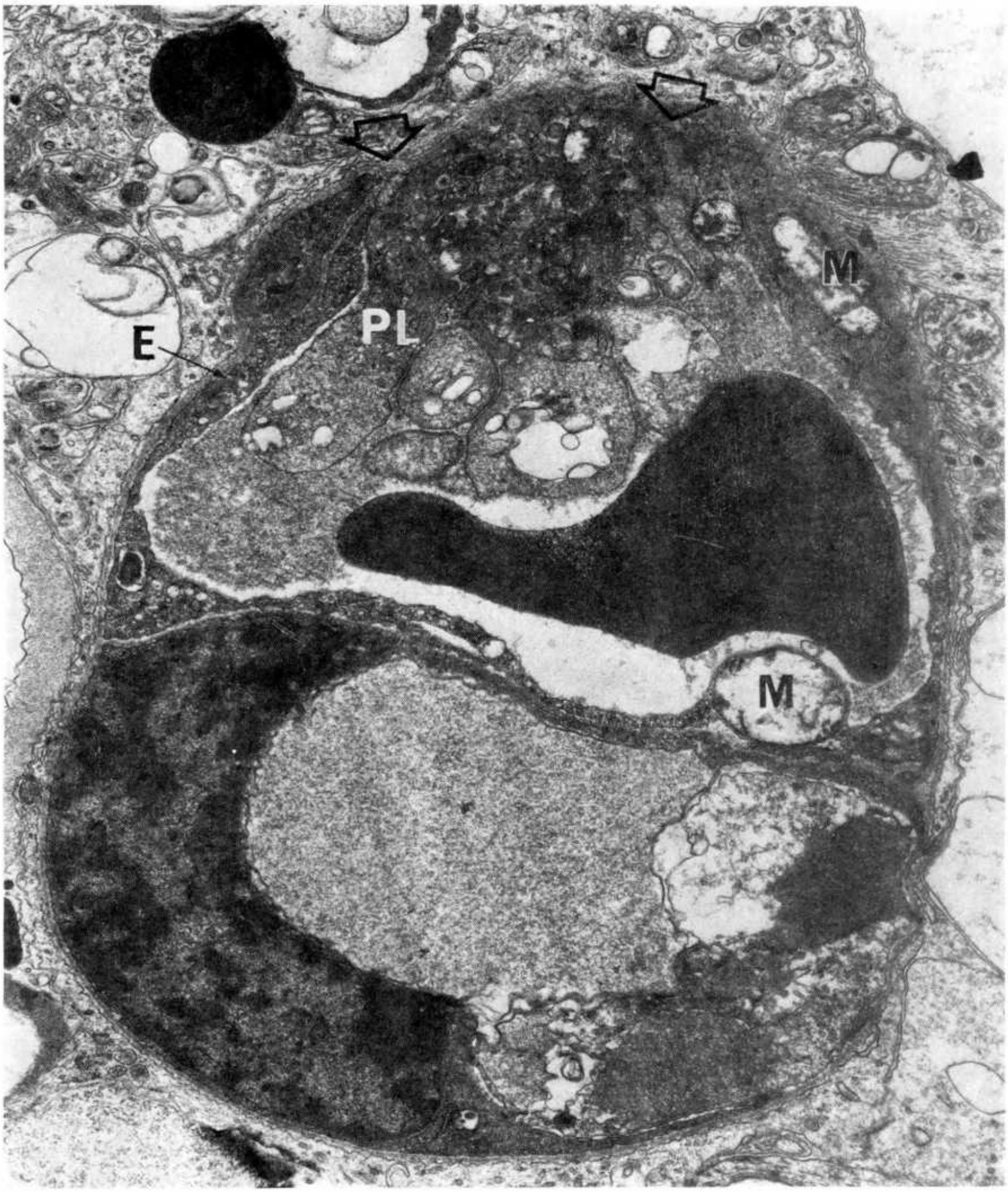


Fig. 5 *Platelets (PL) in a degenerate capillary at 7 h after occlusion. The endothelium (E) is thin and electron-dense with swollen mitochondria (M) and there is a break in the region indicated by broad arrows. Electron micrograph (× 14 000)*

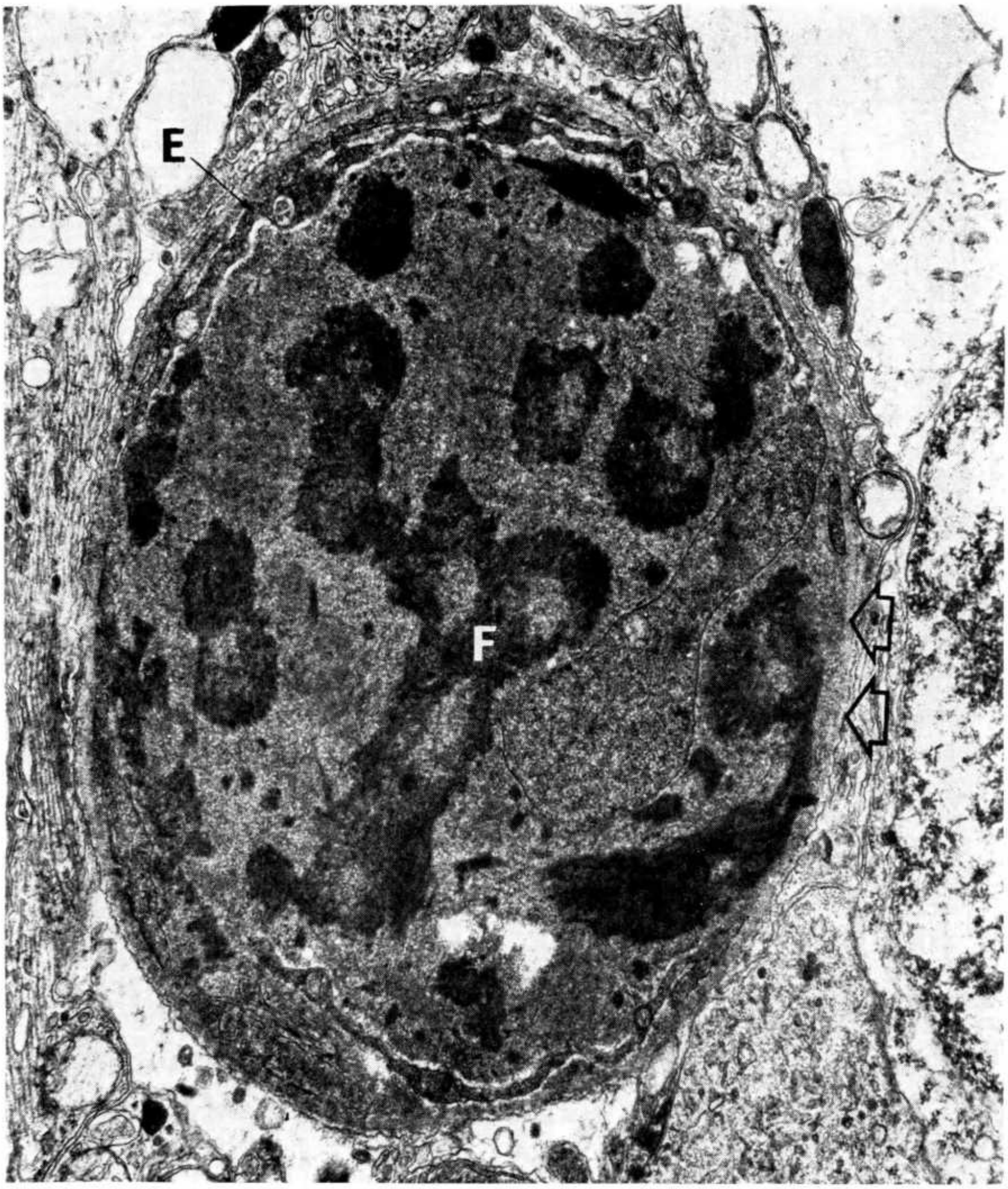


Fig. 6 *Capillary totally occluded by a thrombus of fibrin (F) and dense plasma. The endothelium (E) is thin and absent in places (arrows). 7 h after occlusion. Electron micrograph (× 24 000)*

at a distance of several millimetres from the site of occlusion. Furthermore, the endothelium and muscle cells of the corresponding artery were also slightly vacuolated. There were large intra- and subretinal haemorrhages in the region of the vein, and there was an extensive subretinal exudate with proliferation of the pigment epithelium. No marked changes were seen in the choroid; a small area of the choriocapillaries appeared to be blocked with lysed erythrocytes and cell debris but the larger vessels were all undamaged.

The actual site of occlusion was not examined at times later than 7 days. However, in the later specimens the occluded vein and its branches were highly degenerate at some distance from the site of occlusion. These abnormalities are further described under *(b)* retinal vascular changes.

(b) *Retinal vascular changes (eyes 22, 32, 33, 41)*
The carbon-perfused flat preparation of a retina 7 days after occlusion (No. 32) showed the greater calibre of the veins in the occluded half than in the nonoccluded half. The veins were particularly dilated and tortuous in the region temporal to the macula, and in this area there was evidence of considerable leakage from the small vessels. The capillaries in the occluded half were also more conspicuously filled with carbon than their counterparts in the superior, unaffected part of the retina. There were no areas of the retina in which the vessels did not contain carbon, and therefore the occlusion in this instance had not given rise to any large areas of capillary closure. A digest preparation of the same perfused retina did not reveal any marked changes in the capillaries, though the peripheral vessels in the occluded half contained more fragments of red blood cells and probably more eosinophilic pericyte nuclei than the vessels unaffected by occlusion.

Sections of retinae at 7 and 14 days after occlusion showed many capillaries engorged with red blood cells (Fig. 7). The erythrocytes were often fragmented or lysed, and some were located in the capillary wall (Figs. 7 and 8). The endothelium and pericytes were always degenerate and often they were virtually absent, so that the capillary wall consisted of little more than basement membranes (Fig. 7). Gaps or discontinuities in the basement membrane were only rarely seen, and usually the basement membranes appeared to restrain the enclosed erythrocytes. One break was found in the wall of a large venule or vein, and this appeared to be the origin of a large haemorrhage.

At 35 days after occlusion no normal vessels were recognised in the occluded half of the retina. The branches of the occluded vein were totally degenerate and were represented simply by basement membranes. The adjacent artery was also necrotic; the muscle cells and endothelium were virtually absent, so that empty spaces were left between the basement membranes. The endothelium and pericytes of the capillaries were almost totally absent, so that all that remained were the basement membranes (Fig. 9). Some of these basement membrane ghosts of the capillaries were empty channels (Fig. 9), but many were invaded by processes of the Müller fibres or glial cells (Fig. 10). These cell processes surrounded any remnants of plasma or erythrocytes (Fig. 10) and occasionally filled the whole lumen. The processes entered the capillary lumen through small breaks in the basement membranes, and often the spaces formerly occupied by pericytes were also filled with invading glial cell processes. The glial cells inside the capillaries usually contained smooth endoplasmic reticulum, some ribosomes, microfilaments, and small mitochondria, all of which were typical cytoplasmic features of normal Müller fibres (Fig. 10), but in addition they sometimes contained vesicles of lipid, and occasionally the cells had the appearance of macrophages.

A digest preparation of the retina which had been occluded for 35 days confirmed the abnormal appearance of the capillaries. In the occluded half the small vessels were almost totally anucleate where vessels in the unoccluded superior half of the retina appeared normal. The division between the temporal cellular and acellular capillaries was a line corresponding to the horizontal raphe.

(c) *Other retinal changes (Eyes 22, 33, 41)*
At 7 days after occlusion there were extensive areas of haemorrhage in the retina. In some regions the nerve fibre layer was completely replaced by closely packed erythrocytes, and there were also some large accumulations of erythrocytes in the inner nuclear layer and outer plexiform layer. In the other layers and in other regions there were fewer erythrocytes, but they were accompanied by extensive oedema, particularly in the nerve fibre and outer plexiform layers. There was also macular oedema with detachment and loss of photoreceptors. Small areas of subretinal exudate with loss of photoreceptors were found in some other regions of the retina.

In the 14 day specimen there were regions of the retina which were severely damaged by massive intra- and subretinal haemorrhages. In at least one place the inner limiting membrane was ruptured, and erythrocytes and macrophages were present in the vitreous. Other regions of the retina, however, were relatively undamaged, oedema was not a prominent feature, but some small subretinal haemorrhages had caused a partial loss of photoreceptors.

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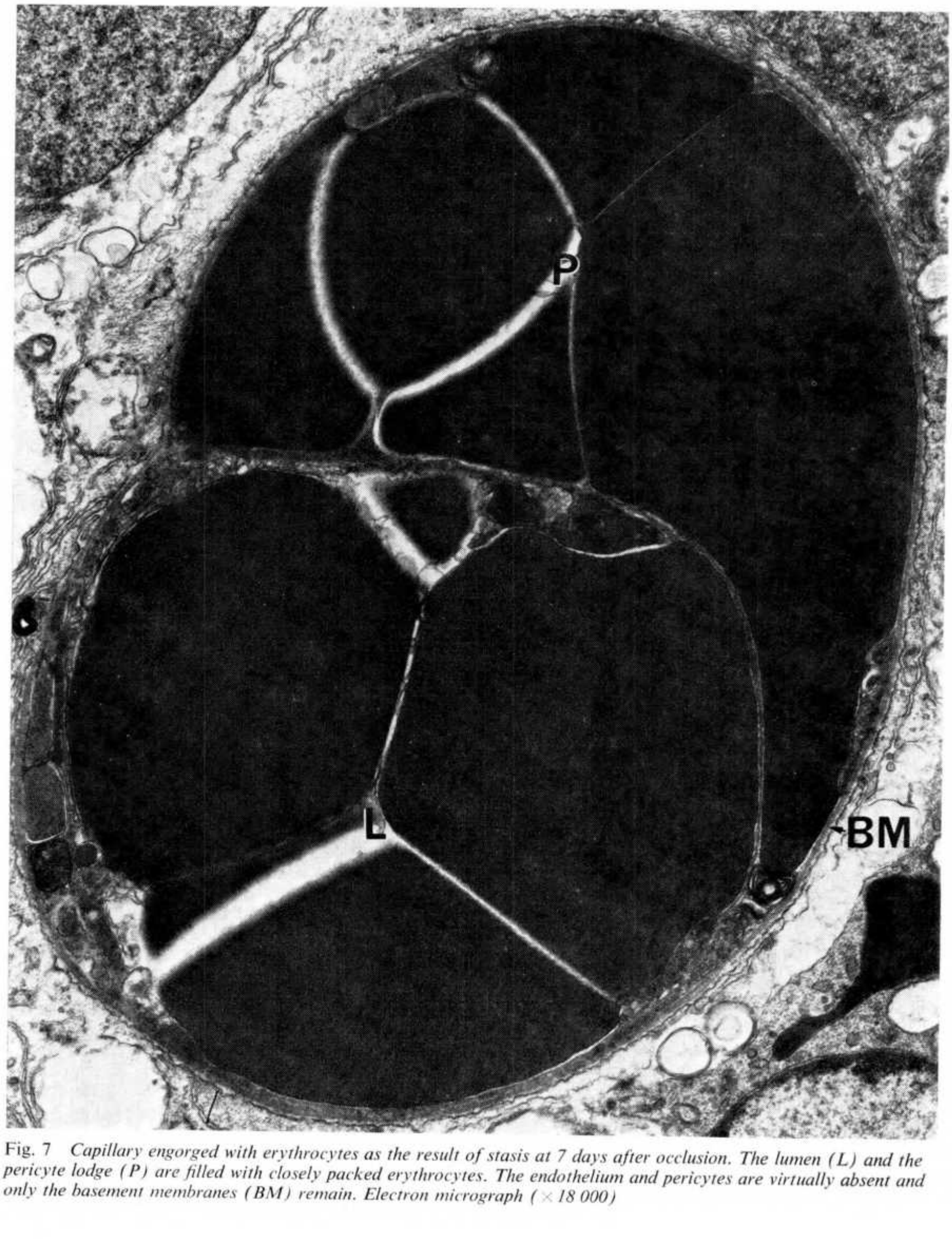

Fig. 7 *Capillary engorged with erythrocytes as the result of stasis at 7 days after occlusion. The lumen (L) and the pericyte lodge (P) are filled with closely packed erythrocytes. The endothelium and pericytes are virtually absent and only the basement membranes (BM) remain. Electron micrograph (× 18 000)*

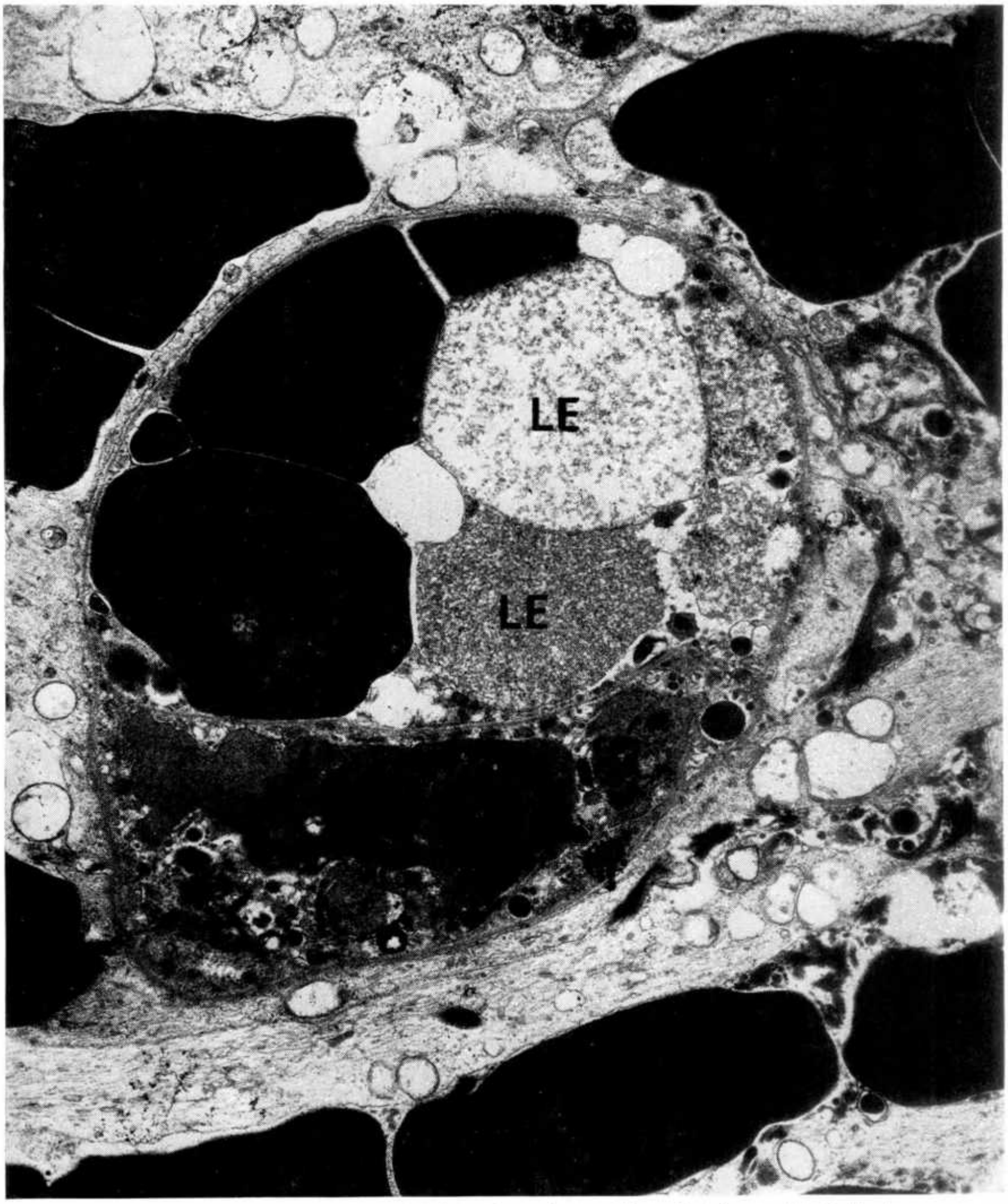

Fig. 8 *Capillary in a region of haemorrhage at 7 days after occlusion. The wall of the vessel is highly degenerate and lysed erythrocytes (LE) are present in the engorged lumen. Electron micrograph (× 10 000)*

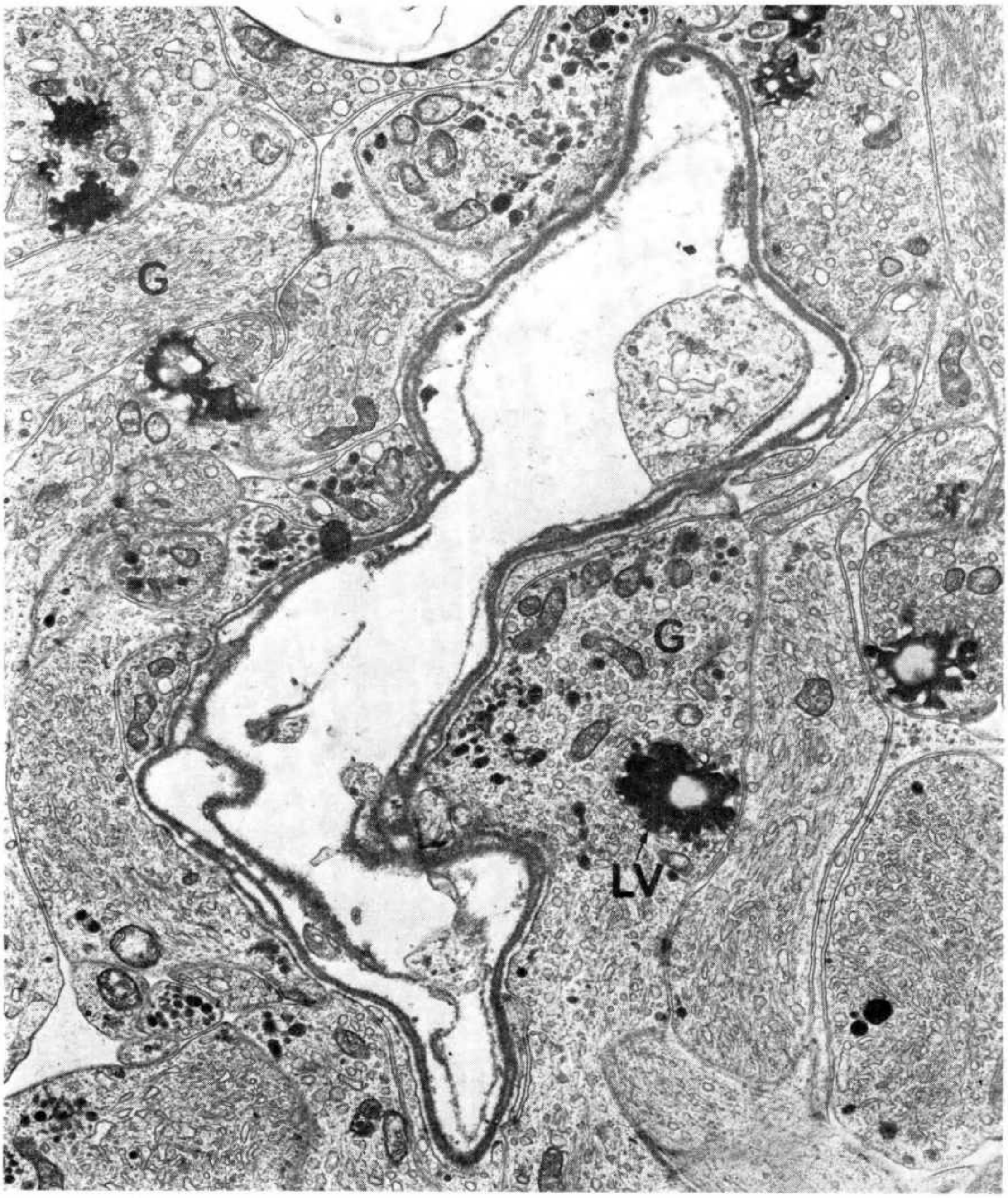

Fig. 9 *Empty basement membrane ghost of a capillary at 35 days after occlusion. The vessel is surrounded by numerous glial cell processes (G) which contain vesicles of lipid (LV). Electron micrograph (× 14 500)*

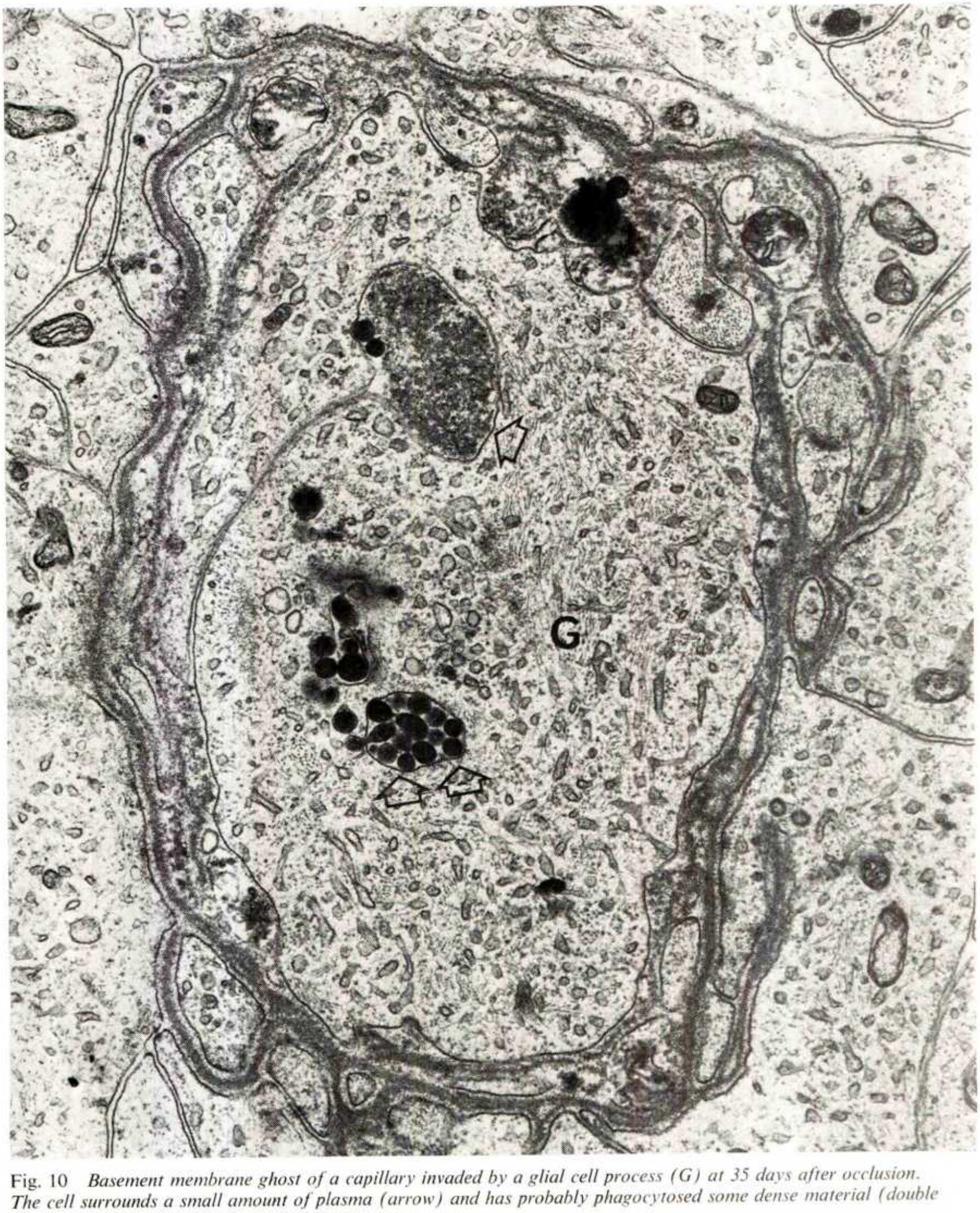

Fig. 10 *Basement membrane ghost of a capillary invaded by a glial cell process (G) at 35 days after occlusion. The cell surrounds a small amount of plasma (arrow) and has probably phagocytosed some dense material (double arrow). Electron micrograph (× 25 000)*

The 35 day specimen again presented areas of severe retinal degeneration and areas of comparatively normal retina, although in all regions the capillaries were highly abnormal. The severely damaged areas were detached and the photoreceptors and outer nuclear layer were absent. The remaining retinal layers were usually recognisable, but in some areas there was further degeneration with the formation of cystic spaces. These regions were invaded by numerous macrophages which contained either lipid or the remains of red blood cells. In the more normal parts of the same occluded retina the photoreceptors and their nuclei appeared to be completely undamaged. The other retinal layers also were relatively normal although there were a few extravascular erythrocytes in the inner layers and the nerve fibre layer was thin and partly replaced by proliferation of glial cells.

Discussion

The histological and electron microscopical observations correlate well with the clinical and fluorescein angiographic pictures in monkeys (Hamilton *et al.*, 1979). All the 7 to 35 day specimens (Nos. 22, 32, 33, 41) which were examined microscopically followed the path of progression with numerous haemorrhages and evidence of capillary closure. No corroborative histological studies have been made on the resolution of the disease.

Examination of the actual site of the occluding laser burn by both light and electron microscopy confirmed the occluded state of the vein. The changes detected in the choroid at the site of occlusion were mostly confined to a small area of the choriocapillaris and were probably insignificant. No damage was detected in the outer layers, and there was no loss of photoreceptors, except at the site of occlusion, until approximately 1 week after occlusion. Therefore it would seem unlikely that the changes in the retina were related to choroidal damage at the site of occlusion.

The microscopical studies have revealed a sequence of 3 major changes in the retinal microvasculature during the period from 1 hour to 5 weeks after vein occlusion. (*a*) Immediately after occlusion (1 to 6 hours) there was leakage from the capillaries in the occluded segment, and this was accompanied by retinal oedema. (*b*) From approximately 6 hours after occlusion there were degenerative changes in the capillaries which would account for delayed perfusion and at this time haemorrhages first appeared in the retina. (*c*) After about a week the capillaries were reduced to basement membrane ghosts and at the same time there was clinical evidence of capillary closure. The origins and interrelationships of these three stages of the disease will now be discussed to illustrate the probable sequence of cytological events resulting in closure and destruction of the capillaries.

(*a*) LEAKAGE AND OEDEMA (1 TO 6 HOURS)

Extravascular deposits of the perfused peroxidase were found in the retinal tissues within 1·5 hours after vein occlusion and a small number of extravascular erythrocytes were also found at the same time. The capillary endothelium and its intercellular junctions normally form an efficient blood-retinal barrier (Ashton, 1965; Ashton and Cunha-Vaz, 1965; Cunha-Vaz and Shakib, 1967), and the alterations induced by vein occlusion which permit leakage are still not fully understood.

A recent review by Ryan and Majno (1977) lists 5 possible cellular changes which may contribute to the pathogenesis of vascular leakage in inflammation. In the absence of endothelial destruction the most likely mechanism appears to be the formation of intercellular gaps by the breakdown of endothelial junctions. Opening of the intercellular junctions also allows escape of erythrocytes from the lung capillaries of guinea-pigs with experimental thrombocytopenia (Dale and Hurley, 1977).

In the present study passage of peroxidase or erythrocytes through the junctions was not seen, but neither was there any evidence of endothelial destruction until 7 hours after occlusion. We conclude, therefore, that at the earlier times leakage probably occurred via endothelial junctions which may have been temporarily disrupted. The possibility also remains that there was focal rhexis of the capillaries which was rapidly repaired and thus not detected. Furthermore, some peroxidase may have escaped from the capillaries via endothelial pinocytotic vesicles.

Tso and Shih (1976) were unable to find any morphological basis for disruption of the blood-retinal barrier in ocular hypotony even though there was leakage from the retinal vessels. Wallow and Engerman (1977), however, have demonstrated peroxidase in the endothelial junctions of retinal vessels from diabetic dogs.

Leakage in the immediate postocclusion specimens was accompanied by intracellular retinal oedema, which can be attributed to the hypoxic conditions resulting from the impaired circulation (Ashton, 1970). Extracellular oedema was initially confined to the outer plexiform layer, presumably because of the ability of this layer to absorb large quantities of fluid and because of the absence of capillaries for reabsorption (Duke-Elder and Dobree, 1967).

(*b*) DEGENERATIVE CHANGES, DELAYED PERFUSION, AND HAEMORRHAGES (6 HOURS TO 1 WEEK)

The earliest morphological change detected in the capillaries was flattening of some of the vessels and the formation of a slit-like lumen. The flattened capillaries were usually found in the deeper layers of the retina and occasionally it appeared that they were compressed by the surrounding oedema, a process which has been described in the retina (Ashton, 1959) and in the brain (Kowada *et al.*, 1968). Perfused peroxidase was always found in the slit-like lumens, and thus the flattened appearance of the capillaries was not associated with complete cessation of capillary perfusion, but it may have contributed to delayed perfusion. The possible role of a rise in tissue tension in causing delayed perfusion cannot be fully evaluated on static, morphological evidence alone since post-mortem compression of the vessels may have occurred. Kohner *et al.* (1970) found that capillaries did not reopen after absorption of retinal oedema.

Following the flattened appearance of the capillaries there were more specific degenerative changes in the endothelium and pericytes. These changes can be positively correlated with delayed perfusion, since they led to thrombus formation. The initial alteration in the cells was swelling of the mitochondria, presumably resulting from the reduced circulation and lack of oxygen. The endothelium was often less severely affected than the pericytes, possibly because of its better oxygen supply and greater distance from the toxic products of other necrotic cells in the retina (Ashton and Tripathi, 1977). There was no evidence of regeneration or proliferation of the endothelium.

A more consistent change in the capillaries at about 6 hours after occlusion was the presence of intramural erythrocytes located beneath the endothelial basement membrane and adjacent to the pericytes. Intramural erythrocytes were always associated with a degenerate appearance of the pericytes. The endothelial cells usually had a more normal appearance, and, as noted earlier, there was no evidence concerning the route of erythrocytes through the endothelium. Movement of large numbers of erythrocytes out of capillaries at 6 hours after occlusion can be correlated with the first appearance of macroscopical retinal haemorrhages at about the same time.

The continuing effects of the sluggish circulation in the later specimens appeared to result in further degenerative changes in the endothelial cells. An increased number of vacuoles appeared in the cells, the endothelium became very thin and electron-dense, and eventually there were endothelial breaks. Necrosis of the endothelium and the resulting exposure of the basement membrane resulted in the formation of platelet thrombi. Fibrin was invariably associated with the platelets and some capillaries with a necrotic endothelium were completely blocked by thrombi of electron-dense plasma and fibrin. Thus capillary degeneration resulted in areas of complete stasis in the microvasculature.

Haemorrhages first appeared in the retina at about the same time as marked capillary degeneration, and they gradually became more severe and involved more retinal layers. Although initially the haemorrhages could not be shown to be associated with rupture of the vessel wall, the massive haemorrhages at later times were clearly associated with morphological breaks in the vessels. The most severe retinal damage occurred in areas where haemorrhages were present in the outer retinal layers and subretinal region. Even after reabsorption of the subretinal blood cells the photoreceptors remained absent.

(*c*) PERMANENT CAPILLARY CLOSURE (1 TO 5 WEEKS)

After the first appearance of thrombi in the capillaries there was clearly stasis in the small vessels and many capillaries were filled and distended with closely packed erythrocytes. Degeneration of the endothelium and pericytes appeared to proceed rapidly in the anoxic conditions associated with stasis and there was also lysis and fragmentation of the blood cells. Eventually acellular, empty basement membrane channels were left which corresponded to the anucleate vessels seen in retinal digest preparations. The closed state of acellular capillaries has been demonstrated by Ashton (1953) and Cogan *et al.* (1961). Closure probably became irreversible after entry of proliferating glial cell processes into the ghost vessels. Breaks in the basement membranes which allowed entry of glial cells were seen infrequently, and the basement membranes appeared to be resistant to degenerative changes. Possibly the glial cell processes entered the vessels through the same breaks which had permitted the earlier haemorrhages.

Regeneration of the endothelium into empty basement membrane tubes could not be identified, and there was no evidence of endothelial proliferation or microaneurysm formation. The requirements for microaneurysm formation, namely, endothelial degeneration with persisting blood flow, were appearently not fulfilled in the healthy young experimental monkeys, at least within the time limits of the present observations. Intraretinal revascularisation after experimental vein occlusion has been described clinically (Hamilton *et al.*, 1979) and by electron microscopy (Hamilton *et al.*, 1975; Archer, 1976); the postocclusion time intervals, however, were usually longer than 35 days.

Conclusion

Our observations on the early stages of the progressive degeneration of capillaries and the accompanying retinal changes which followed vein occlusion can be summarised as a sequence of 7 stages (Table 2). Basically, blockage of the vein resulted in a decreased flow of blood, which produced anoxic conditions in the retina. As a result there were functional and later structural changes in the capillaries. These changes led to thrombus formation and stasis, which was followed by degeneration and finally obliteration of the microvasculature in those monkeys whose retinal circulation remained deficient.

The accompanying retinal changes were also partly explained by the histological findings. Initially there was oedema caused by stagnant flow and leakage from the small vessels. Later, more permanent retinal damage was caused by haemorrhages in the outer layers and subretinal region. Finally, after destruction of the capillaries there was atrophy of the neural elements in the inner retinal layers.

The timing of the different stages of the disease can be given only in general terms, since each monkey was an individual and not strictly part of a series. The individuality of the disease in each monkey was probably a result of the differing degrees of occlusion produced in each animal and the different extents to which the circulation was restored. Nevertheless, from the microscopical studies it would appear that only functional changes occurred in the first few hours following occlusion and that structural changes began to occur after about 6 hours. By 1 week after occlusion the changes in the microvasculature were probably permanent (Table 2).

Table 2 *Experimental retinal vein occlusion: sequence of changes leading to permanent capillary closure*

Time (approx.)	*Capillaries*	*Retina*
1 to 6 hours	1 Stagnation. Dilatation. Leakage ↓ 2 Degeneration of endothelium and pericytes	Oedema. Exudates
6 hours to 7 days	↓ 3 Focal thrombus formation ↓ 4 Stasis ↓ 5 Loss of endothelium and pericytes	Haemorrhages. Capillary nonperfusion
7+ days	↓ 6 Basement membrane 'ghosts' ↓ 7 Glial cell invasion	Proliferation of glia. Resolution of oedema and haemorrhages. Permanent capillary closure

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A comparative study of argon laser and krypton laser in the treatment of diabetic optic disc neovascularisation

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SUMMARY A comparative study of the relative efficacy of the krypton and argon lasers in the treatment of disc new vessels in diabetic retinopathy was made. Resolution of the disc new vessels was achieved in both instances. There were clinical differences in the use and effects of the 2 lasers.

Panretinal photocoagulation is an established method of treatment of proliferative diabetic retinopathy in eyes with optic disc neovascularisation (Cheng *et al.*, 1976). However, marked shrinkage of visual fields often follows xenon-arc treatment because the burns frequently affect the nerve fibre layer of the retina (Hamilton *et al.*, 1976). The ruby laser, although it does not give such field constriction, proves to be successful in only 21% of eyes (Aiello *et al.*, 1968). The argon laser photocoagulator was developed by L'Esperance (1968) so as to render precise control of the beam diameter, exposure time, and power. It is now widely used in the management of proliferative diabetic retinopathy and is particularly effective where neovascularisation involves the optic disc (Diabetic Retinopathy Study Research Group, 1976).

The krypton laser photocoagulator differs from the argon laser photocoagulator in that it emits a red beam with a wavelength of 647·1 nm as opposed to a blue-green beam with the main wavelengths of 488·0 and 514·5 nm with the argon laser. Therefore, theoretically little energy from the krypton laser is absorbed by haemoglobin, which precludes direct coagulation of retinal blood vessels (François and Cambie, 1977) (Fig. 1).

The purpose of this study is to compare the effectiveness of argon laser photocoagulation with krypton laser photocoagulation in the treatment of diabetic optic disc neovascularisation by panretinal photocoagulation.

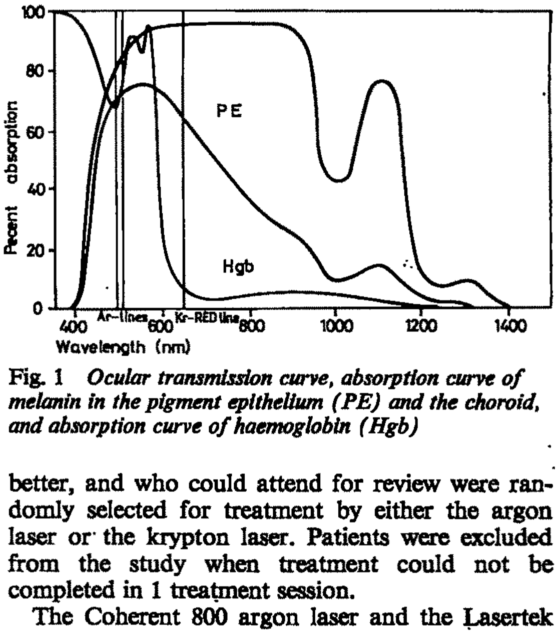

Fig. 1 *Ocular transmission curve, absorption curve of melanin in the pigment epithelium (PE) and the choroid, and absorption curve of haemoglobin (Hgb)*

Patients and methods

Patients seen in the diabetic clinic with neovascularisation involving the optic disc, a vision of 6/9 or better, and who could attend for review were randomly selected for treatment by either the argon laser or the krypton laser. Patients were excluded from the study when treatment could not be completed in 1 treatment session.

The Coherent 800 argon laser and the Lasertek krypton laser were used for treatment. The selection of treatment was in accordance with a pre-existing randomised list. The new blood vessels on the optic disc were graded according to the Hammersmith classification of disc neovascularisation (Kohner *et al.*, 1971). The method of treatment was by the technique of pan-photocoagulation, and this was completed in 1 session, a minimum of 2000 burns being applied (Hamilton *et al.*, 1976). The 200-μm spot size was used around the posterior pole and the 500-μm spot size further out in the periphery up to and beyond the equator. With both instruments the timing was set at 0·2 second and the intensity was adjusted until a 'light burn' was achieved.

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Table 1 *Results*

	Visual acuity			*Effect of treatment at 2 days*					
	Pretreatment	*10/52 Post-treatment*	*Number of burns*	*Myopia*	*Shallow AC*	*Annular choroidal detachment*	*Initial grade of vessels*	*Grade at 10 weeks*	*Complications*
Argon									
1	6/9	6/9	2327	–	–	–	3	1	
2	6/9	6/18	2012	–	–	–	2	2	Vitreous haemorrhage
3	6/9	6/9	2028	+	+	+	3	0	
4	6/9	6/12	2052	–	–	–	5	3	Vitreous haemorrhage
5	6/5	6/5	2024	–	–	–	2	0	
6	6/5	6/5	2004	–	–	–	4	0	
Krypton									
1	6/9	6/9	2005	+	+	+	5	0	
2	6/6	6/6	2000	+	+	+	2	0	
3	6/9	6/9	2013	–	–	–	3	2	
4	6/9	6/18	2037	+	+	+	5	3	Vitreous haemorrhage
5	6/9	6/9	2015	+	+	+	3	0	
6	6/5	6/5	2003	–	–	–	5	0	

Patients were evaluated initially, and at 1, 3, and 10 weeks. Corrected visual acuity and visual fields were tested, fluorescein angiography was carried out, and colour photographs were taken. In addition they were also examined on the second day after treatment for macular oedema, annular choroidal detachment, and anterior chamber depth.

Results

Twelve eyes in 8 patients qualified for the study. Six eyes were treated by the argon laser and 6 by the krypton laser.

VISUAL ACUITY

The majority of eyes retained their pretreatment visual acuities at 10 weeks after treatment. Vision deteriorated in only 3 eyes during the study owing to vitreous haemorrhages developing from persistent new vessels on the optic disc (Table 1).

ANTERIOR CHAMBER DEPTH

Examination on the second postoperative day showed shallow anterior chambers in 4 eyes treated by the krypton laser and in 1 eye treated by the argon laser, and all 5 eyes had an associated annular choroidal detachment. In none of the eyes with shallow anterior chamber and annular choroidal detachment was there any evidence of raised intraocular pressure. All 5 eyes showed a deterioration of their visual acuities and had myopia ranging from –0·5 to –1·0 dioptres. Return to the previous refraction occurred 1 week after treatment. In no patients was macular oedema observed after treatment.

VISUAL FIELDS

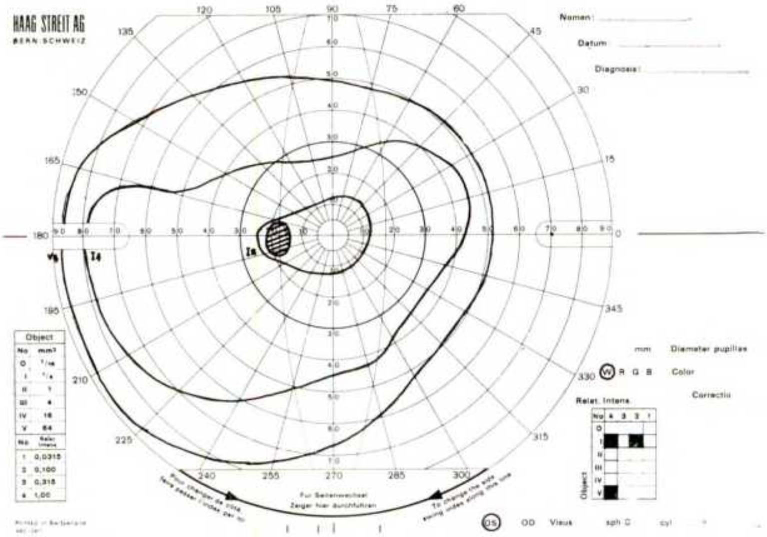
Perimetry was done on the Goldmann perimeter with 3 different white targets.

Objective	V	I	I
Intensity	4	4	2

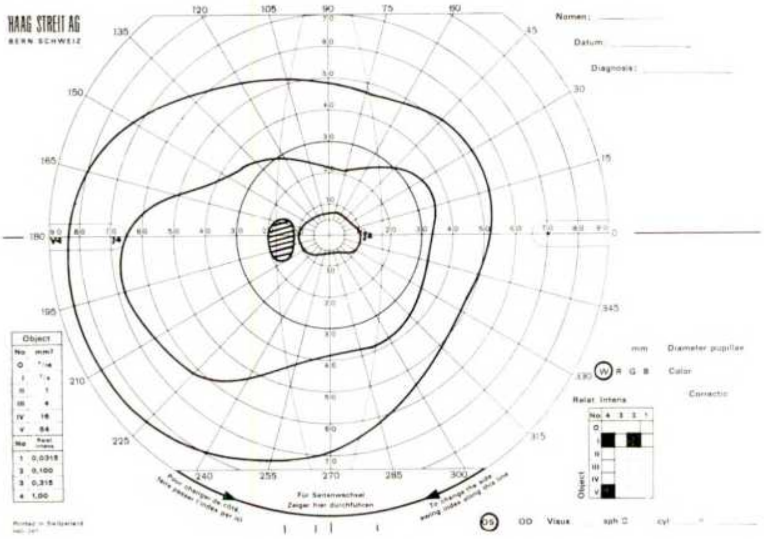
The visual fields remained unchanged for V/4 throughout the study. There was an average centripetal shrinkage of 7 degrees for I/4 in both groups 1 week after treatment and 10 degrees for I/2. Ten weeks after treatment both groups showed some recovery of their visual fields, though it was more pronounced in the krypton-treated group with an

Table 2 *Average centripetal field shrinkage 1 week and 10 weeks after treatment*

		V/4	*I/4*	*I/2*
Argon	1 week	0°	7°	10°
	10 weeks	0°	5°	9°
Krypton	1 week	0°	7°	10°
	10 weeks	0°	3°	7°



2a



2b

Figs. 2a, b *Pretreatment visual field and 10-week post-treatment field in an argon-treated eye*

average centripetal shrinkage of 7 degrees for I/2 and 3 degrees for I/4 compared to 9 degrees and 5 degrees, respectively, in the argon laser-treated group (Table 2; Figs. 2 and 3).

NEOVASCULARISATION ON OPTIC DISC

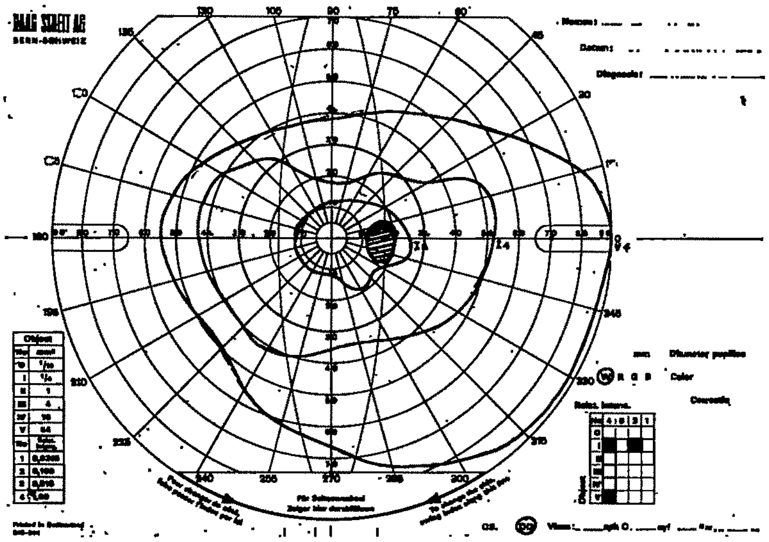
Resolution of new vessels on the optic disc occurred in both groups in the study period (Figs. 4 and 5). In several eyes it was observed in both groups that the new vessels were not perfused when examined on the second day after treatment. This observation did not guarantee total regression of the disc vessels.

There was incomplete resolution of new vessels in 3 eyes belonging to the argon laser-treated group and 2 eyes in the krypton laser-treated group at the end of the study period (Table 1). Three of these eyes developed vitreous haemorrhages.

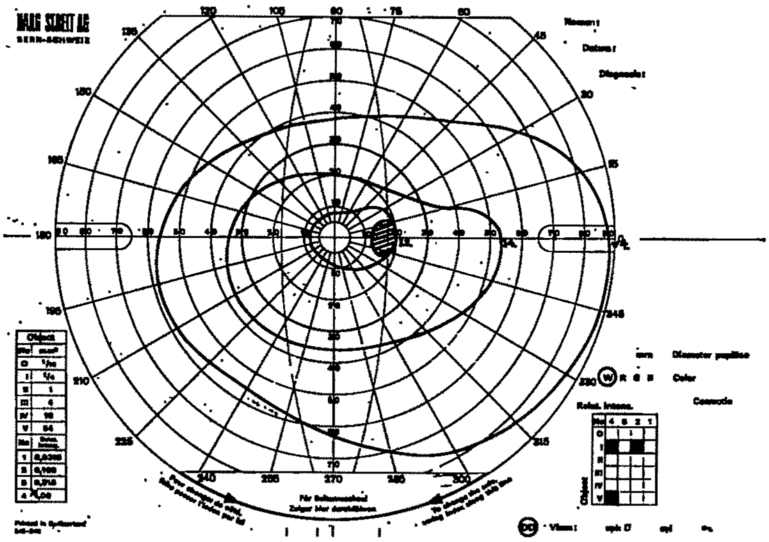
SIDE EFFECTS

Patients treated with the krypton laser more frequently complained of pain during treatment. In 3 patients in which 1 eye was treated with the krypton laser and the second eye with the argon laser a prominent subjective finding was that treatment

3a



3b



Figs. 3a, b *Pretreatment visual field and 10-week post-treatment visual field in a krypton-treated eye*

with the krypton laser was more painful. This observation was also found in subsequent patients not recruited into this study.

COMPLICATIONS

On 3 occasions with the krypton laser heavy burns resulted in small haemorrhages, almost certainly derived from the choroidal circulation and developed from the outer border of the pigment halo surrounding the burn.

The bleeding stopped within a few seconds and did not spread into the retrovitreal space. None of the patients receiving argon laser coagulation developed haemorrhages.

With the krypton laser inadvertent coagulation of blood vessels produced no spasm of the vessel or haemorrhages. With the argon laser particular attention was applied to avoiding retinal blood vessels because of the known complication of spasm and haemorrhage from inadvertent coagulation (Hamilton *et al.*, 1976).

The average centripetal field shrinkage is smaller in the krypton laser-treated group after the 10-week period. Although the difference is small, its

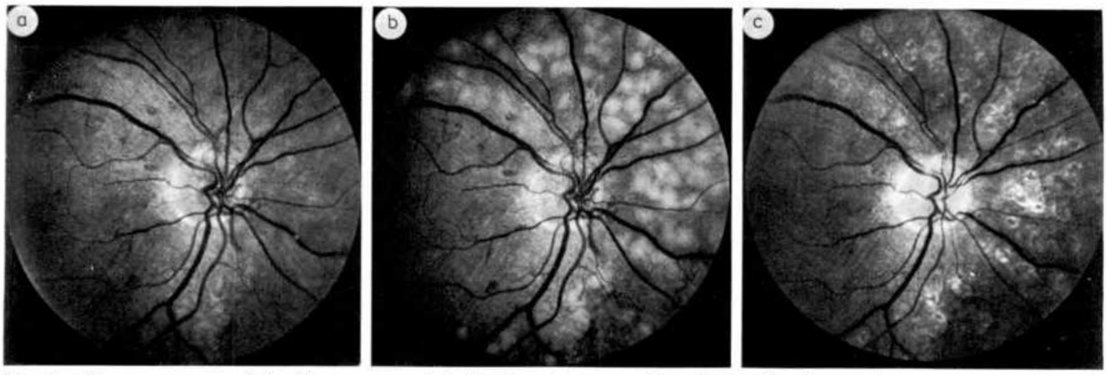


Fig. 4 *The appearance of the disc new vessels* (a) *before treatment;* (b) *within a few hours of treatment;* (c) *10 weeks after treatment in an argon-treated eye with complete regression of disc vessels*

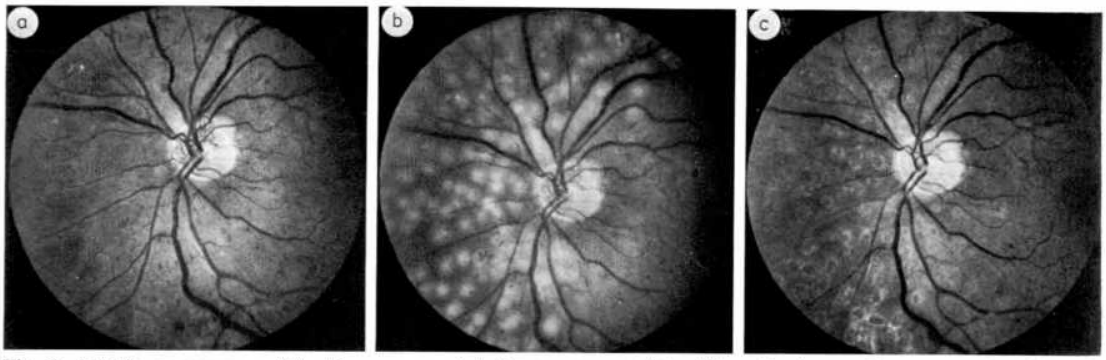


Fig. 5 (a) *The appearance of the disc new vessels before treatment;* (b) *within a few hours of treatment;* (c) *10 weeks after treatment in a krypton-treated eye with complete regression of the new vessels*

significance and subsequent evolution is not yet established.

Discussion

From this limited study the krypton laser appears to be as effective as the argon laser in causing regression of optic disc neovascularisation in diabetics, and throughout this study no difference was found in the response after photocoagulation. The krypton laser wavelength theoretically has a low absorption of energy by haemoglobin, and therefore coagulation of retinal capillaries and larger retinal blood vessels does not seem to be of importance (Marshall and Bird, in preparation). Thus the success of treatment appears to depend upon the effective absorption of energy by the pigment epithelium. Because of the absence of absorption by haemoglobin the krypton laser cannot be used for the direct coagulation of new vessels. In addition, if a haemorrhage occurs during treatment it is not possible to stop the flow of blood by coagulating the bleeding area.

Of note is the high instance of annular choroidal detachment in the krypton-treated group, and this is of clinical importance because of the possibility of the precipitation of closed-angle glaucoma after treatment.

The increased incidence of annular choroidal detachment in the krypton group may be a direct result of the more penetrating krypton burn affecting the larger choroidal vessels (Marshall and Bird, in preparation).

A subjective significant finding was that treatment with the krypton laser was more painful, and it may be advisable to use a retrobulbar anaesthetic, especially when treatment is planned to be completed in 1 session. Once again this may be due to the greater penetration of the krypton burn.

The krypton laser requires further evaluation to establish the effect on retinal blood vessels and also on the optic disc. In view of the lack of absorption by haemoglobin it may be of use in the treatment by panretinal photocoagulation of patients with mild to moderate vitreous haemorrhages.

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Treatment of amoeboid herpetic ulcers with adenine arabinoside or trifluorothymidine

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SUMMARY In previous studies adenine arabinoside and trifluorothymidine were found to be equally effective treatments for dendritic ulcers of the cornea, but a trend emerged which suggested that in amoeboid ulcers trifluorothymidine was more effective. The collection of additional cases confirms the superiority of trifluorothymidine in such cases.

Despite extensive research 5-iodo-2′-deoxyuridine (IDU) has remained until recently the only antiviral agent generally available to clinicians for treating ulcerative herpetic keratitis.

Adenine arabinoside (Ara-A) and trifluorothymidine (F_3T) (Wellings *et al.*, 1972; Pavan-Langston, 1975; Coster *et al.*, 1976) are both highly effective in treating herpetic corneal ulceration. In a large series of herpetic ulcers treated with one or other of these agents no difference could be found in the dendritic ulcer group (Fig. 1), but a trend emerged which suggested that F_3T had some advantage over Ara-A in treating the less common but more severe amoeboid ulcers (Coster *et al.*, 1976).

Not only are amoeboid ulcers less common than dendritic ulcers, they have often been treated with steroids before referral to an ophthalmologist, and many have associated stromal disease and uveitis. They constitute the most difficult therapeutic challenge for antiviral drugs used for ulcerative epithelial herpetic keratitis. Cases of this type are therefore more likely to show a difference in effectiveness between 2 highly active antiviral compounds than the less challenging cases of dendritic ulcer.

In the initial trial 102 patients were treated—87 with dendritic ulcers, 15 with amoeboid ulcers (Coster *et al.*, 1976). A further 15 amoeboid ulcers were treated under the same protocol in an effort to clarify the trend which seemed to be emerging in the initial study. This paper reports the results.

Patients and methods

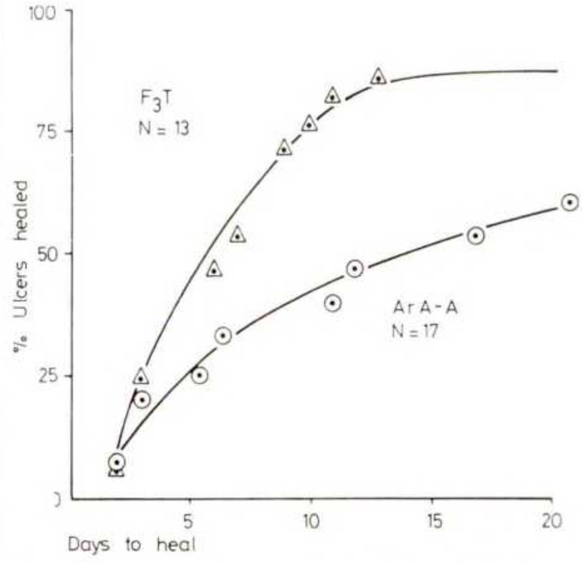

Fig. 1 *Cumulative frequency graph of times for healing of dendritic ulcers under treatment with 3% adenine arabinoside ointment or 1% trifluorothymidine eye drops 5 times daily*

Thirty unselected patients with typical amoeboid ulcers who consented to enter the study were included. All completed the course of treatment; 17 were treated with Ara-A and 13 with F_3T.

The coded treatments were randomly allocated by the pharmacist within closely matched strata. The stratification was based on the features considered to be related to poor prognosis. These were: the size of the epithelial defect, whether the patient had been treated with steroids before coming to hospital, and whether or not the patient was atopic.

All patients were treated on an outpatient basis. The coded preparations consisted of either 3·3% Ara-A ointment or 1% F_3T drops, which were

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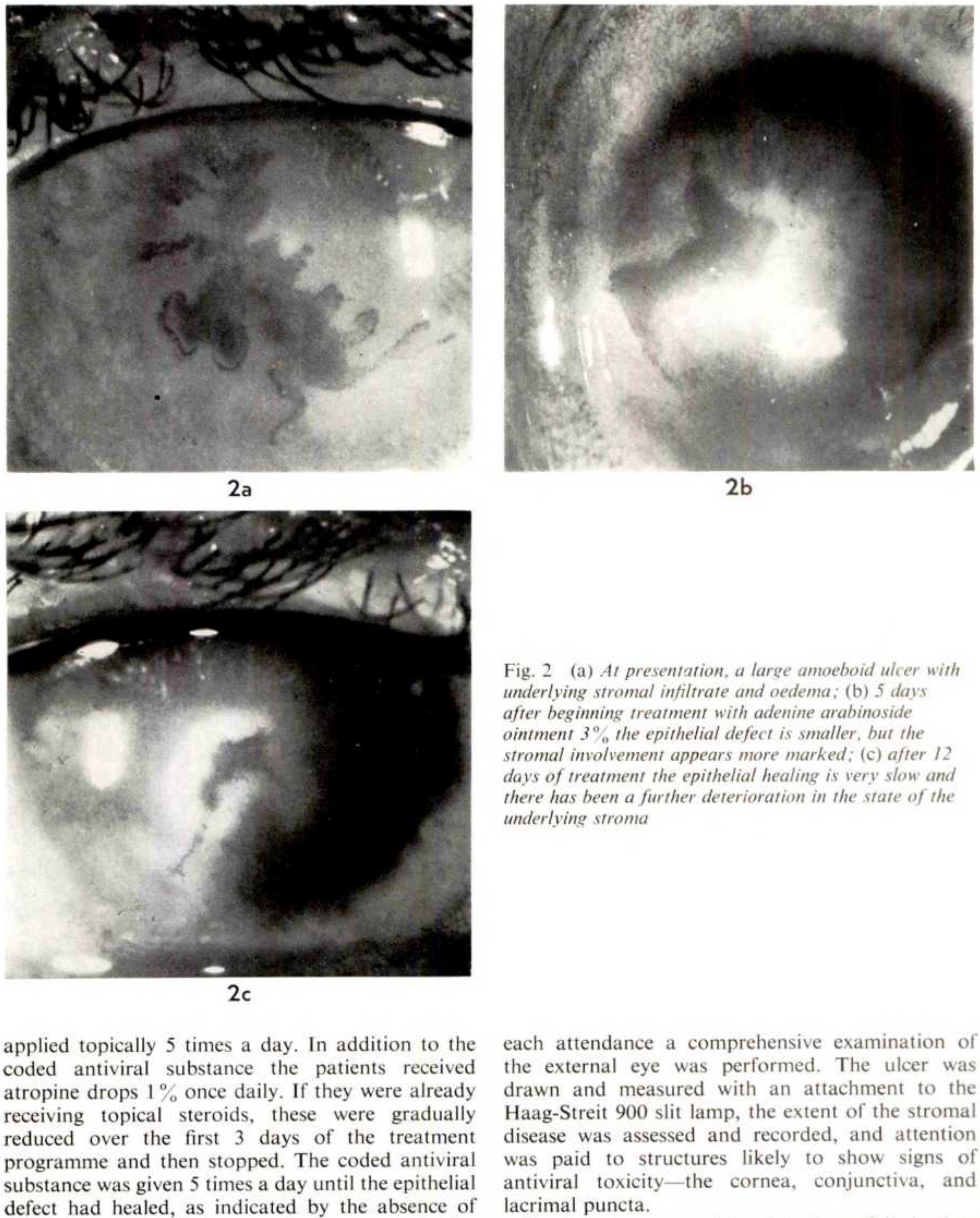

2a

2b

2c

Fig. 2 (a) *At presentation, a large amoeboid ulcer with underlying stromal infiltrate and oedema;* (b) *5 days after beginning treatment with adenine arabinoside ointment 3% the epithelial defect is smaller, but the stromal involvement appears more marked;* (c) *after 12 days of treatment the epithelial healing is very slow and there has been a further deterioration in the state of the underlying stroma*

applied topically 5 times a day. In addition to the coded antiviral substance the patients received atropine drops 1% once daily. If they were already receiving topical steroids, these were gradually reduced over the first 3 days of the treatment programme and then stopped. The coded antiviral substance was given 5 times a day until the epithelial defect had healed, as indicated by the absence of staining with fluorescein. The frequency of administration was then reduced to 3 times a day for an additional 3 days.

Patients were reviewed on alternate days, and at each attendance a comprehensive examination of the external eye was performed. The ulcer was drawn and measured with an attachment to the Haag-Streit 900 slit lamp, the extent of the stromal disease was assessed and recorded, and attention was paid to structures likely to show signs of antiviral toxicity—the cornea, conjunctiva, and lacrimal puncta.

Treatment was considered to have failed when the epithelial defect had not healed after 21 days, had failed to decrease in size, or had enlarged over 3 successive visits.

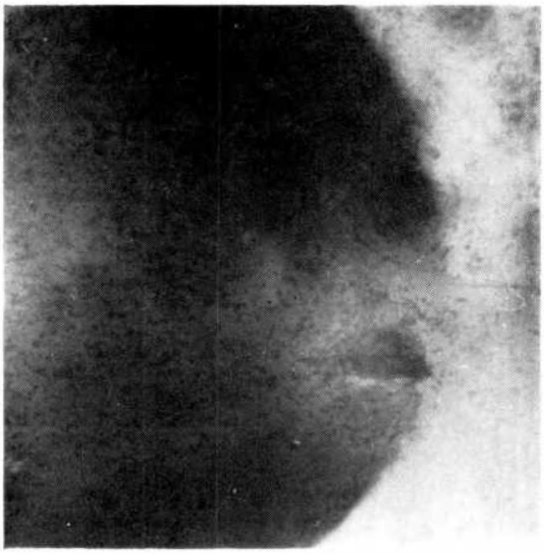

Fig. 3 *Slit-lamp photograph of the cornea stained with 1% Bengal rose after 20 days' treatment with trifluorothymidine. The ulcer has failed to heal and there is widespread superficial punctate keratopathy indicative of antiviral toxicity. The ulcer healed rapidly after the antiviral was withdrawn*

Results

In 6 patients the ulcers failed to heal. Four were treated with Ara-A and 2 with F$_3$T. The pattern of failure was different in the 2 treatment groups. The failures on Ara-A treatment showed epithelial healing initially, but the stromal disease progressed with failure of the epithelium to continue healing (Figs. 2*a*, 2*b*, and 2*c*).

One patient treated with F$_3$T showed good healing initially, developed punctate epithelial staining with Bengal rose after 10 days, and despite the absence of stromal disease failed to heal until the antiviral treatment was withdrawn (Fig. 3). The other failure on F$_3$T had severe stromal disease when entered into the trial. This gradually improved, and the epithelium healed on the twenty-fourth day, 3 days after the arbitrary 'closing date' beyond which treatment was considered to have failed.

Standard actuarial survival curves, or cumulative distribution curves, provide the most accurate and easily assimilated statement of the time taken to heal by ulcers in each group. The logrank test is the most appropriate for assessing differences between groups as displayed on the survival curves. The test is the most powerful available, being effective when dealing with quite small samples (Peto and Peto, 1972). In addition it can be used to assess differences between groups of patients when the groups are defined not only by treatment schedule but by any factor thought to influence prognosis such as size of ulcer and extent of stromal disease (Mantell and Haenszell, 1959). An additional advantage is that it is not a parametric test and does not assume that the healing times follow a normal distribution. The distribution of healing times is set out in Fig. 4, and clearly does not follow such a distribution.

A logrank analysis was performed on the data set out above. It indicates that the difference between the 2 treatment groups is likely to be significant ($P = 0{\cdot}05$). The results are displayed in Fig. 5.

COMPLICATIONS AND DRUG REACTIONS

Apart from failure to heal, complications were few. The only recurrence in the immediate post-treatment

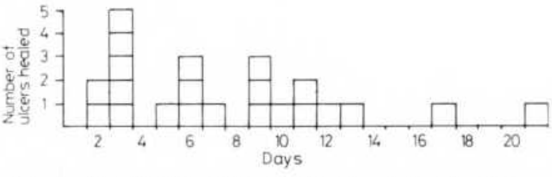

Fig. 4 *Distribution of times of healing of amoeboid ulcers treated with either adenine arabinoside or trifluorothymidine*

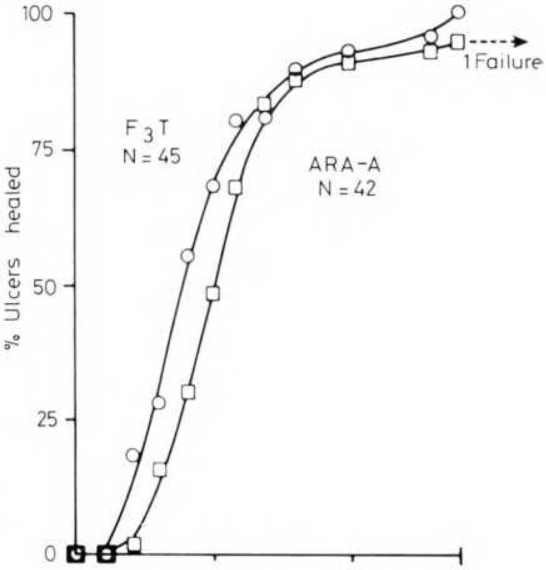

Fig. 5 *Cumulative frequency graph of times of healing of amoeboid ulcers treated with either 3% adenine arabinoside ointment or 1% trifluorothymidine eye drops 5 times daily*

phase occurred in a patient treated with Ara-A; a small epithelial defect developed 13 days after the initial ulcer had healed and 10 days after treatment had ceased.

Stromal disease progressed in 4 patients, all of whom had been treated with Ara-A: the epithelial defect failed to heal, and these cases were designated treatment failures.

The only manifestation of antiviral toxicity observed was punctate staining of the corneal epithelium with Bengal rose. This occurred in 3 patients treated with Ara-A and 4 treated with F_3T; in one of the latter the epithelial defect failed to heal until the F_3T was withdrawn (Fig. 3).

Discussion

These results indicate that F_3T is more effective than Ara-A in dealing with amoeboid ulcers. The superiority of F_3T over Ara-A in the treatment of amoeboid ulcers, when no difference could be found in the dendritic ulcer group, reflects important differences between these 2 conditions. We were able to compare the patterns of these conditions during a period in which patients with dendritic or amoeboid ulcers were admitted to a treatment trial under the same protocol (Coster *et al.*, 1976). In addition to the obvious difference in the size of the epithelial defect it was evident that, in comparison with dendritic ulcers, amoeboid ulcers occurred more often in patients who had been treated with topical steroids before coming to hospital and were more often complicated by stromal disease and uveitis. The duration of symptoms before coming to hospital was longer in the amoeboid group (Table 1). No difference was evident with regard to sex or age of patients.

The apparent superiority of F_3T over Ara-A in the treatment of such ulcers may be due to superior antiviral activity of F_3T in the corneal epithelium, or it may be related to a more pronounced effect of this compound against stromal virus. The compounds may differ in their transepithelial absorption into the corneal stroma, or alternatively the large epithelial defect of amoeboid ulcers may allow greater stromal uptake of the more-water-soluble F_3T than with the less-water-soluble Ara-A.

The results of this trial have obvious implications for the clinician. They also indicate the need for stratifying, randomising, and ranking the nature of the epithelial defect and the extent of deep disease of the corneal stroma and uvea when planning clinical trials of antiherpetic agents.

Herpetic corneal ulceration has provided an important proving ground for antiviral compounds with clinical potential, the disease providing a wide range of therapeutic challenges. After debridement, ulcers, with their reduced viral load, provide the opportunity to demonstrate antiviral activity in low-potency agents (Jones *et al.*, 1976). Dendritic ulcers are appropriate for showing differences in more active compounds, and amoeboid ulcers provide the highest order of clinical challenge, capable of sorting out clinically important differences in activity between highly active compounds.

Table 1 *Differences in distribution of pretreatment with steroids, stromal disease, uveitis, and length of history before presentation at hospital between patients with dendritic and amoeboid ulcers*

	Dendritic ulcers (n = *87*)	*Amoeboid ulcers* (n = *30*)
Pretreated with steroids	19 (22%)	16 (53%)
Stromal disease at presentation	39 (45%)	27 (90%)
Uveitis at presentation	28 (32%)	19 (63%)
Symptoms for more than 2 weeks prior to presentation	14 (16%)	13 (43%)

We thank our colleagues at Moorfields Eye Hospital, City Road, London, who referred the cases. Mr R. Watkins, Chief Pharmacist, supervised the allocation to treatment groups. The adenine arabinoside was supplied by the Parke Davis Company, Ann Arbor, Michigan, USA, and the trifluorothymidine by the Wellcome Foundation, Beckenham, Kent. The figures included were prepared by the Audio-Visual Department of the Institute of Ophthalmology, London, and Fig. 1 is reproduced by courtesy of the University of Chicago Press.

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Acycloguanosine: antiviral activity in the rabbit cornea

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SUMMARY We describe experiments, using the multiple microinoculation technique, to produce superficial herpes simplex keratitis in the rabbit cornea, which showed a potent antiviral effect of acycloguanosine.

Although they are usually effective for the treatment of epithelial herpes simplex keratitis, idoxuridine (IDU), adenine arabinoside (ara-A), and trifluorothymidine (F_3T) have limitations of solubilities and toxicity which render them inadequate for the management of deep herpetic disease. Acycloguanosine (Wellcome 248U) shows promise of overcoming these limitations. It is soluble in water (as the sodium salt), and has low toxicities from both topical ocular and systemic administration in several animal species (Schaeffer *et al.*, 1978; Tucker *et al.*, 1978) and man. It has potent antiviral activity against herpes simplex virus (HSV) types I and II, both in vitro and in vivo (Elion *et al.*, 1977; Bauer *et al.*, 1979).

As a preliminary to our first clinical trial of 248U, which has now been completed (Jones *et al.*, 1979), and in order to compare data from our own laboratory with those of others (Bauer *et al.*, 1979) we investigated the efficacy and tolerability of 248U in our rabbit corneal lesion inhibition system (Falcon and Jones, 1977a).

Methods

Details of the multiple microinoculation technique of Jones and Al-Hussaini, and of its modification to produce a corneal epithelial lesion inhibition assay, are published elsewhere (Jones and Al-Hussaini, 1963; Falcon and Jones, 1977a). In summary, 25 circular sites are inoculated on each eye of anaesthetised adult Dutch rabbits by means of a capillary tube of 1 mm diameter filled with pH 8 strain of HSV (of $1{\cdot}5 \times 10^6$ plaque-forming units/ml). Treatment generally begins 2 hours after inoculation and is administered 5 times daily. 48 hours after inoculation each site is scored 0 to 4 according to the number of sites infected, and a corneal epithelial lesion inhibition assay (CELIA) is produced by comparing treated with control eyes in groups of 3 or 4 rabbits (which gives statistically valid results). The advantage of this lesion-inhibition system is that the lesions are small and discrete at the time of scoring, which provides rapid, accurate, and repeatable results from the minimum of animals, and the experiment can be terminated before the eyes have become uncomfortable.

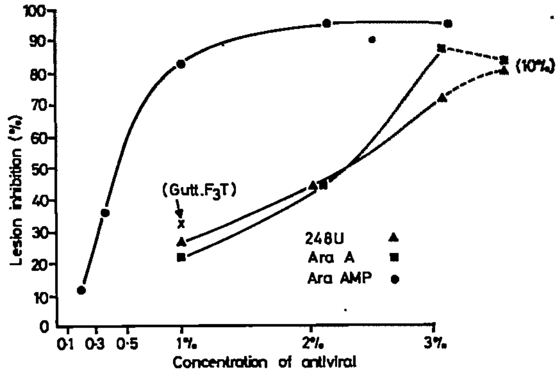

Fig. 1 *Dose/response curves for 248U, ara-A and ara-AMP ointments. Treatment was given 5 times daily, starting 2 hours after inoculation. Eyes scored 48 hours after inoculation*

Results

Experiments were performed to give a dose/response curve for 248U ointment. This was compared with ara-A ointment, and ara-A 5′ monophosphate (ara-AMP) ointment, which had been shown previously to give greater lesion inhibition than any other antiviral tested in this system (Falcon and Jones, 1977b). It was also compared with standard 0·5% IDU ointment and with 1% F_3T drops (Fig. 1).

We had shown previously that a single dose of

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ara-AMP given directly after inoculation had an almost catastrophic lesion-inhibiting effect, whereas IDU, ara-A, or F_3T had little effect (Falcon and Jones, 1977b). 248U was employed in the same system and likewise had very little effect (Fig. 2).

In experiments to investigate the effect of systemic 248U, 50 mg/kg of 248U was given intravenously twice daily, the injections starting 2 hours after inoculation, and this experiment was continued for 72 hours. At 48 hours there was a small difference in scores between treated and control animals, and this had increased very considerably by 72 hours (Fig. 3).

Although this model, and particularly the scoring system, were derived primarily for lesion-inhibition experiments, we attempted to use them to assess therapy of established lesions: treatment began 48 hours after inoculation and was given 5 times daily. Scoring was carried out immediately before the beginning of the treatment and subsequently after 3 and 5 more days. We compared control, oculentum IDU 0·5%, oculentum ara-A 1%, oculentum ara-AMP 1%, guttae ara-AMP 1%, guttae F_3T 1%, and guttae 248U 1%. It proved impossible to produce meaningful scores, since the lesions 48 hours from inoculation had already spread away from the inoculation sites. We therefore merely scored each eye as 'healed' or 'unhealed' (Table 1).

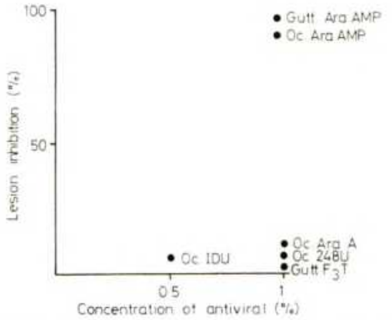

Fig. 2 *Lesion inhibition from single doses of various antivirals. Treatment was given once immediately after inoculation, and the eyes were scored 48 hours later*

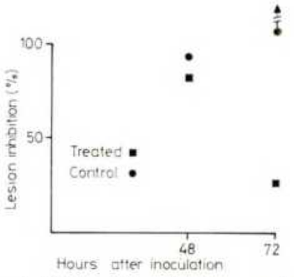

Fig. 3 *Lesion inhibition 48 and 72 hours after inoculation: 50 mg/kg of 248U was given intravenously twice daily, starting 2 hours after inoculation*

Table 1 *Number of eyes healed (out of 3 in each group), 3 and 5 days after start of antiviral treatment, which was given 5 times daily, starting 48 hours after inoculation*

Antiviral	*Number healed*	
	At 3 days	*At 5 days*
Control	0	0
Oculentum IDU 0·5%	0	0
Oculentum Ara A 1%	0	0
Oculentum Ara AMP 1%	0	0*
Guttae F_3T 1%	2	3
Guttae 248U 1%	3	3

* Severe toxic epitheliopathy at this stage

Discussion

Fig. 1 shows that the dose/response curves for 248U and ara-A are very similar, and it shows that the efficacy of 1% and 2% 248U ointment, as measured by lesion inhibition, is comparable to that of 1% F_3T drops. The dose/response curve for ara-AMP indicates a substantially superior antiviral effect, but this has been shown to be due to the unique and profound lesion-inhibiting effect of ara-AMP when given shortly after inoculation (Falcon and Jones, 1977b) (Fig. 2). ara-AMP has proved too toxic for practicable clinical application to the eye.

These lesion-inhibiting experiments thus indicate a useful potential for topical 248U, which is supported by our experiments in the treatment of established lesions (Table 1), though these have emphasised the limitations of this method.

Our experiments with intravenous 248U therapy demonstrate an encouraging antiviral effect in the cornea, although, as might be expected, this is delayed in comparison with the effect of topical treatment. Experiments are now in progress to establish a model of deep herpetic keratitis and to investigate the role of subconjunctival and systemic 248U therapy for it. These routes may prove to be the most effective means of achieving a good intraocular level of the drug, since very low aqueous levels of 248U were obtained after its application to the cornea, whether or not the epithelium was breached (Bauer, personal communication). The water solubility and low toxicity of 248U should provide no barriers to such therapy and indeed offer possibilities for safe and effective therapy of herpes virus infections throughout the body.

We are indebted to the following: Wellcome Research Laboratories Ltd., Beckenham, for provision of 248U; Parke-Davis & Co., Ann Arbor, Michigan, USA, for provision of Ara A and Ara AMP; Mr R. Watkins, chief pharmacist, and staff, who prepared the antivirals; and Dr P. Collins, Wellcome Laboratories, for provision of HSV pools.

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Efficacy of acycloguanosine against herpetic ulcers in rabbit cornea

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SUMMARY The effect of a new antiherpetic compound of very low toxicity called acycloguanosine (Wellcome 248U) on herpetic ulcers in rabbit cornea was studied by the Corneal Epithelial Lesion Therapeutic Assay (CELTA). The therapeutic effect of 3% acycloguanosine ointment on dendritic ulcers was equal to that of 0·5% 5-iodo-2′-deoxyuridine (IDU) ointment. No toxic symptoms could be detected by slit-lamp on 4 days' treatment with this concentration of acycloguanosine. Because of its selective action on virus only, its extremely low toxicity in animals, and its availability for systemic administration, acycloguanosine seems to be an ideal antiviral compound for use in the treatment not only of herpetic keratitis but also of other herpetic diseases in man.

Herpes simplex virus (HSV) is one of the main infectious causes of eye disease in industrialised countries. IDU, first shown to be effective by Kaufman *et al.* (1962), has been the main drug used in the treatment of herpetic keratitis. However, cases that fail to respond to IDU or that develop allergic or toxic signs have been reported (Pavan-Langston and Dohlman, 1972; McGill *et al.*, 1974; Hyndiuk *et al.*, 1975), and so other antivirals are required. Adenine arabinoside (ara-A) and trifluorothymidine (F$_3$T) appeared to be suitable alternatives several years ago and they have in fact proved effective against ulcerative herpetic keratitis (Pavan-Langston and Dohlman, 1972; Wellings *et al.*, 1972).

However, ara-A is scarcely soluble in water and has little effect on deep herpetic keratitis by topical application, while F$_3$T, though more soluble and effective than ara-A or IDU, is rather unstable and very expensive. Furthermore these 3 compounds all affect the replication of normal cells, causing some degree of toxicity. Thus more suitable antivirals are required for the treatment of HSV infections.

A possible candidate for this purpose is a guanine derivative called acycloguanosine (Wellcome 248U) (Fig. 1). This drug has marked antiviral activity on HSV and extremely low toxicity, so that it may be administered systemically (Schaeffer *et al.*, 1978; Kaufman, 1978). In this study the efficacy of acycloguanosine against HSV was verified and the therapeutic effect of the drug against ulcerative herpetic keratitis in rabbit cornea was compared with that of IDU by the Corneal Epithelial Lesion Therapeutic Assay (CELTA), a method which gives an indication of the action of antiviral drugs in large-scale clinical trials (Shiota, 1979).

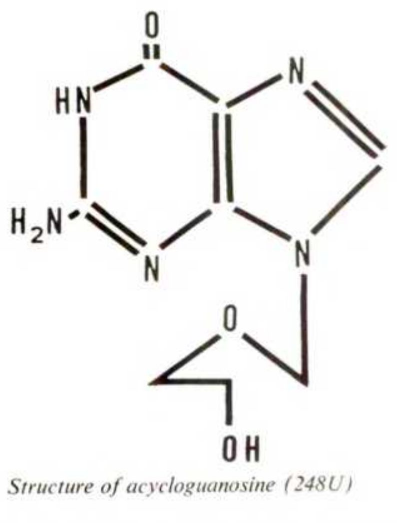

Fig. 1 *Structure of acycloguanosine (248U)*

Methods and materials

Pigmented rabbits weighing between 2·0 and 3·0 kg were used. For inoculation of virus a modification of the multiple microtrephination method of Jones and Al-Hussaini (1963) was used. Rabbits were anesthetised with intravenous pentobarbital sodium (30 mg/kg) and given a retrobulbar injection of

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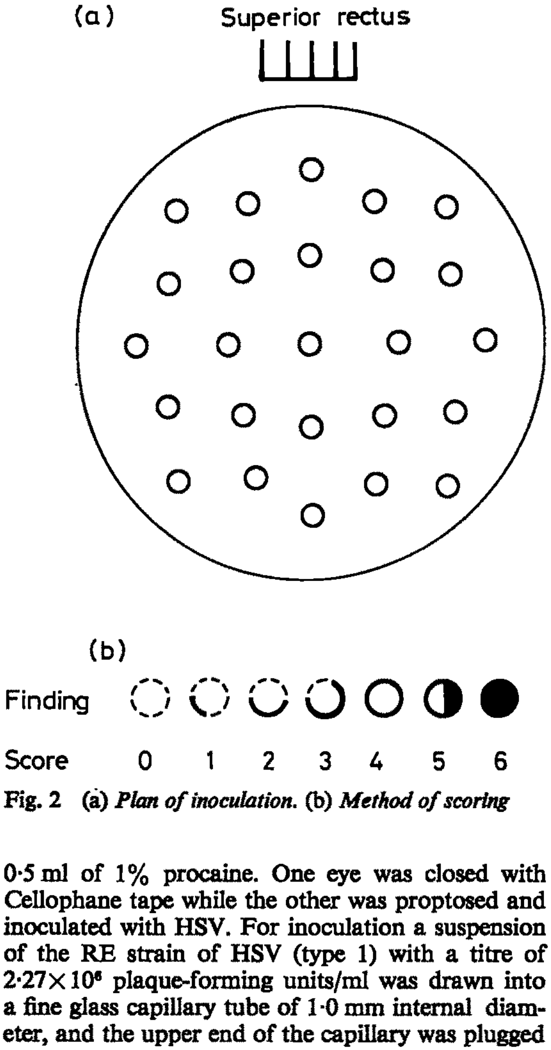

Fig. 2 (a) *Plan of inoculation.* (b) *Method of scoring*

0·5 ml of 1% procaine. One eye was closed with Cellophane tape while the other was proptosed and inoculated with HSV. For inoculation a suspension of the RE strain of HSV (type 1) with a titre of $2{\cdot}27\times10^{6}$ plaque-forming units/ml was drawn into a fine glass capillary tube of 1·0 mm internal diameter, and the upper end of the capillary was plugged with Plasticine.

CELTA METHOD

Trephinations through the corneal epithelium with the capillary tube were made at 25 sites in the cornea (Fig. 2*a*) as for the corneal epithelial lesion reduction assay (Falcon and Jones, 1977). After inoculation the eye was left open for 30 seconds and then the lids were closed with Cellophane tape. The same procedure was repeated on the other eye. In one group of 4 rabbits the right eyes were treated with 3% acycloguanosine ointment and the left eyes with 0·5% IDU ointment, or vice versa. In another group 4 eyes received no treatment as controls. The treatment was started 48 hours after inoculation and continued every 2 hours during the daytime 5 times a day for 4 days. The eyes were examined 48 hours after inoculation and then every 24 hours with a photo-slit lamp after applying 1% Bengal rose, which stains plaques of HSV-replicating cells in the corneal epithelium (Jones and Patterson, 1967). Each inoculation site was scored 0 to 4 according to the extent of the circumference infected, and 1 or 2 was added if half or the whole of the cornea in the circle was ulcerated. Thus each site gave a score of between 0 and 6 as illustrated in Fig. 2*b*. The total daily score for each eye was calculated and expressed as a percentage of the score (percentage score) immediately before treatment. The therapeutic efficacies of acycloguanosine and IDU against ulcerative herpetic keratitis were compared by calculating their average per centage scores.

Results

At 48 hours after HSV inoculation large dendritic ulcers extending along almost the whole circumference infected at each site were seen in all eyes as shown in Fig. 3*a*, and the mean total score per eye was 95·6. In control eyes these ulcers developed steadily, forming wide geographic ulcers with prominent corneal oedema and severe ciliary injection by 6 days after inoculation, as shown in Fig. 3*b*. In contrast, in eyes treated with 3% acycloguanosine ointment the large dendritic ulcers gradually became smaller. After treatment with acycloguanosine for 3 days these lesions became punctate, and after treatment for 4 days they became minute and some sites did not show any lesions at all (Fig. 3*c*). Infected eyes were thus nearly or completely cured by 4 days' treatment with acycloguanosine. Treatment with 0·5% IDU ointment caused the same clinical improvement as treatment with acycloguanosine. A representative eye after 4 days' treatment with IDU is shown in Fig. 3*d*.

These results are summarised in Table 1 and Fig. 4. The antiviral efficacy of 3% acycloguanosine ointment on ulcerative herpetic keratitis appeared to be

Table 1 *Percentage scores of severity of herpetic ulcers in rabbit cornea*

Days of treatment	*3% 248U (n=4)*	*0·5% IDU (n=4)*	*Control (n=4)*
0	100	100	100
1	82·1±17·0	83·4±12·7	105·5±11·4
2	40·7±7·0	45·5±8·4	83·4±21·9
3	26·7±5·7	25·5±2·3	89·3±27·3
4	20·3±8·7	20·3±5·8	122·2±20·9

Treatment was started 48 hours after HSV inoculation

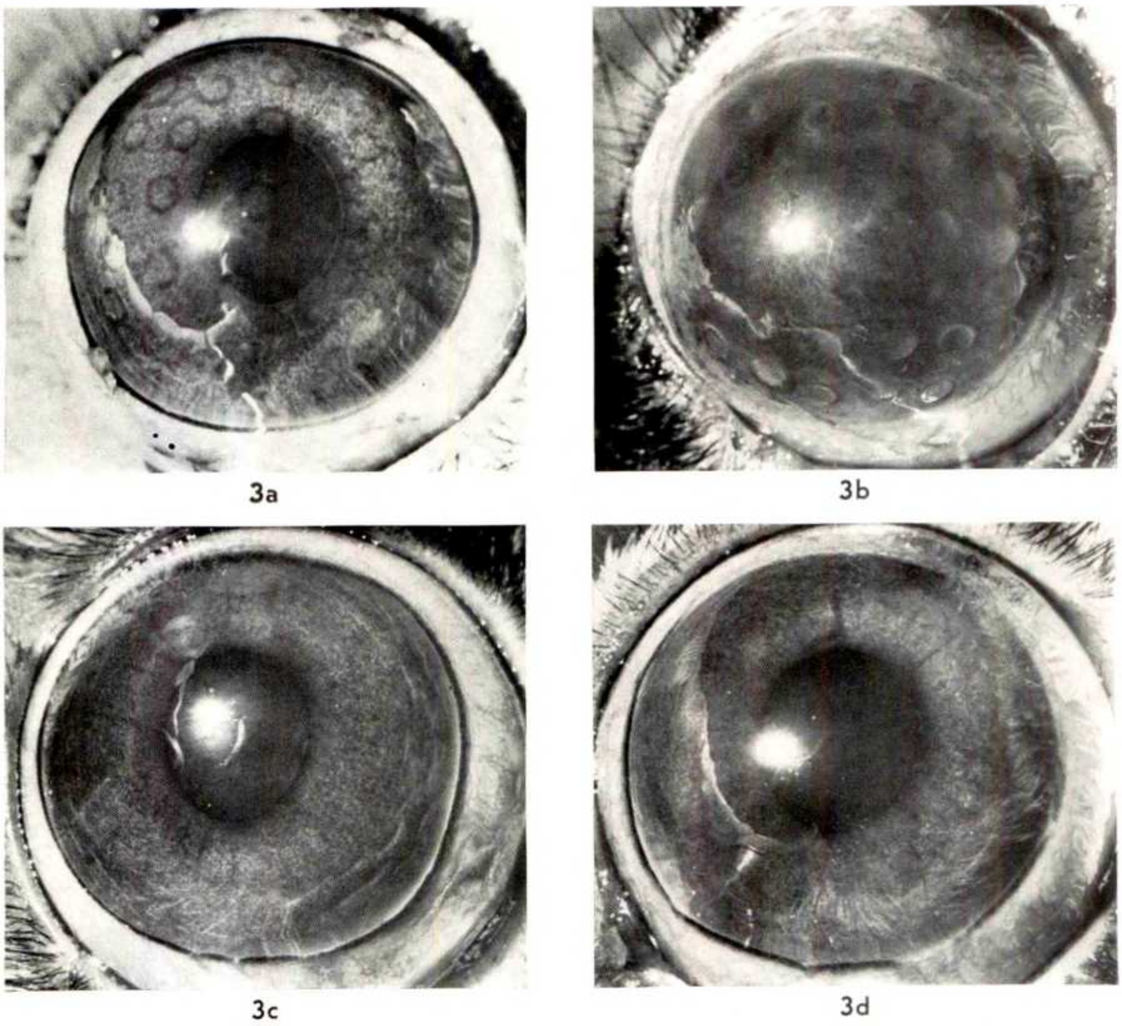

Fig. 3 *Responses of herpetic ulcers in rabbit cornea to acycloguanosine and IDU.* (a) *Eye before treatment, 48 hours after inoculation.* (b) *Control eye 6 days after inoculation.* (c) *Eye treated with 3% acycloguanosine (248U) ointment for 4 days.* (d) *Eye treated with 0·5% IDU ointment for 4 days*

equal to that of 0·5% IDU ointment. No signs of toxicity were detectable by slit lamp during treatment with either drug.

Discussion

We have shown that acycloguanosine was highly effective for treating herpetic ulcers and that the effect of 3% acycloguanosine was similar to that of 0·5% IDU. These findings are in good accord with those of Kaufman (1978). However, Pavan-Langston *et al.* (1978) reported from similar experiments on rabbits that the therapeutic efficacy of 3% acycloguanosine was significantly better than that of 0·5% IDU and 3% ara-A. Kaufman also reported that acycloguanosine was effective against herpetic iritis when given systemically or subconjunctivally (1978). Moreover, Schaeffer *et al.* (1978) found that acycloguanosine was effective against herpetic keratitis in rabbits by topical application, against herpetic encephalitis in mice *per os*, and against cutaneous herpetic infections in guinea-pigs.

Particular attention should be paid to the mode of the selective action of this compound. Acyclo-

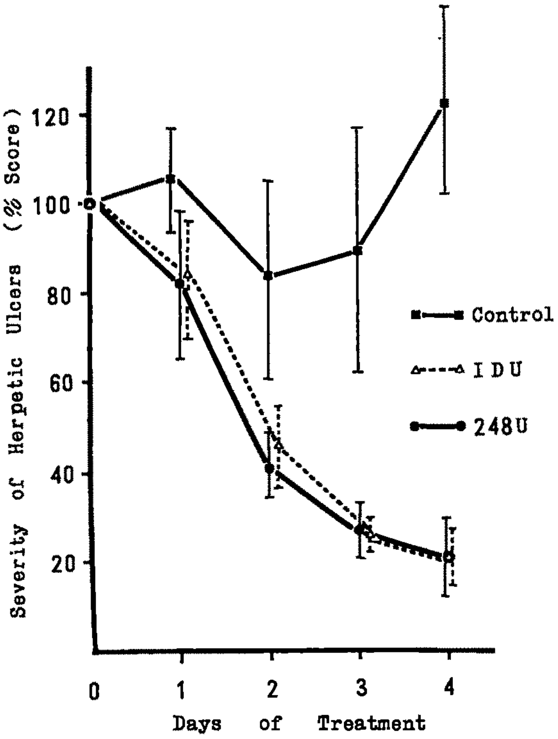

Fig. 4 *Therapeutic effects of acycloguanosine (248U) and IDU against herpetic ulcers in rabbbit cornea: 3% 248U and 0·5% IDU ointment were applied 5 times a day starting 48 hours after HSV inoculation. Four eyes were subjected to each treatment*

guanosine is phosphorylated by a virus-specified thymidine kinase and converted to acycloguanosine triphosphate, which inhibits viral DNA polymerase (Elion *et al.*, 1977). Since acycloguanosine is not appreciably phosphorylated by cellular kinase, it does not affect host cells and thus has extremely low toxicity. In addition Schaeffer *et al.* (1978) found that it is not metabolised when given systemically.

From the facts that acycloguanosine has marked antiviral activity but extremely low toxicity, and that it can be administered systemically and is not metabolised on systemic administration, this drug should be ideal for treatment not only of herpetic keratitis but also of other herpetic infections in man.

We are indebted to Wellcome Research Laboratories, Kent, UK, and Professor Barrie R. Jones, University of London, for provision of 3% 248U ointment; Mr M. Okumoto for provision of the RE strain of HSV; Dr M. Imai, Dr T. Ogawa, and Mrs Y. Endo for technical assistance.

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Treatment of experimental herpes simplex keratitis with acycloguanosine

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SUMMARY Acycloguanosine, a recently developed compound with high inhibitory activity against viruses belonging to the herpes group, has been evaluated in experimental herpes simplex keratitis in rabbits in comparison with trifluorothymidine and preparations of idoxuridine and vidarabine at present in clinical use. All compounds were used in the form of ophthalmic ointments which were applied 5 times a day at intervals of 2 hours. Treatment began on the third day of infection and was continued for 4 days. Complete cure was obtained with acycloguanosine and idoxuridine; trifluorothymidine and vidarabine were considerably less effective. Acycloguanosine was equally effective when given intravenously in the form of its sodium salt, and could be detected in the tear fluid in inhibitory concentrations when given by mouth. The compound was relatively free from toxicity.

The use of specific antiviral agents is an established form of treatment for herpes simplex keratitis, but in many cases treatment is ineffective or gives rise to hypersensitivity and toxic manifestations. These have been summarised by McGill *et al.* (1976). Treatment with idoxuridine may cause contact dermatitis, punctate epithelial keratopathy, follicular conjunctivitis, and thickening of the lid margins associated with stenosis or occlusion of the punctum. Trifluorothymidine may cause contact dermatitis, punctate epithelial keratopathy, and oedema of the corneal epithelium. The same signs of toxicity have been observed with vidarabine, and there is a further report that trifluorothymidine may cause filamentary keratosis (Coster *et al.*, 1976). These drugs also have the disadvantage of not being effective by systemic routes of administration.

The present paper describes a new compound, acycloguanosine, having a number of favourable properties which may make it a useful addition to the range of drugs at present available for the treatment of herpes simplex keratitis.

Acycloguanosine [9-(2-hydroxyethoxymethyl)-guanine] is an acyclic nucleoside possessing high inhibitory activity against certain viruses of the herpes group, including herpes simplex and varicella-zoster. Its antiviral activity and general properties have been described by Schaeffer *et al.* (1978), and are summarised in Tables 1 and 2, which include comparative data for 3 other compounds used in the treatment of herpes simplex keratitis. The antiviral activities were determined by means of plaque reduction dose-response lines carried out with a type 1 strain of herpes simplex virus in VERO cell cultures. From these lines are obtained the values for the ED50, which is the concentration of compound in μM which will reduce the number of plaques to 50% of that in an untreated control preparation. In Table 1 it will be seen from the ED50 values that acycloguanosine is 10 times as active as idoxuridine, 16 times as active as trifluorothymidine, and 160 times as active as vidarabine against the strain of virus used. It therefore has a considerable advantage over these other compounds in respect of its higher antiviral activity.

Table 1 *Relative potencies of acycloguanosine and standard antiherpes simplex compounds*

Compound	*ED50 (μM)*	*Relative potency**
Acycloguanosine	0·1	10
Idoxuridine	1·0	1
Trifluorothymidine	1·5	0·67
Vidarabine	16·0	0·06

*Relative to idoxuridine = 1

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Table 2 *Properties of acycloguanosine and standard antiherpes simplex compounds*

	Acycloguanosine	*Idoxuridine*	*Trifluorothymidine*	*Vidarabine*
Aqueous solubility (%)	0·14	0·8	>5	0·05
Stability of solution at pH 7	Stable	Stable	Unstable	No information
Metabolites	Essentially unmetabolised	Inactive	Inactive	Less active
Enters aqueous	Yes	Yes	Yes	Yes*
Crosses blood-brain barrier	Yes	No	No information	Yes

*As metabolite with reduced activity

General properties and some aspects of the clinical pharmacology of the compounds are compared in Table 2. Low solubility is a disadvantage except in the case of trifluorothymidine, but acycloguanosine forms a sodium salt with an aqueous solubility of 2% which is suitable for intravenous injection. It is catabolised only to the extent of less than 5%, so that practically all the compound is present as the active form. It is present in the blood and urine after oral administration in laboratory animals and human volunteers, and can be found in the tear fluid after intravenous and oral administration of the sodium salt. One hour after oral administration to a dog in a dose of 25 mg/kg acycloguanosine was present in the aqueous in a concentration 20 times greater than the 100% inhibitory concentration as established with type 1 herpes simplex virus in tissue culture (de Miranda *et al.*, 1978).

These generally favourable properties make acycloguanosine a suitable candidate for clinical trial, and as a preliminary its antiviral effect was evaluated in rabbits infected on the cornea with herpes simplex virus, and the results are described in the present work as a comparative study with trifluorothymidine and commercially available ophthalmic preparations of idoxuridine and vidarabine. Also described are the results of preclinical toxicity tests in which the ocular safety of acycloguanosine was evaluated in several species of animals treated topically and by parenteral routes of administration.

Materials and methods

EXPERIMENTAL HERPES SIMPLEX KERATITIS

Ophthalmic preparations

In initial experiments acycloguanosine was administered as aqueous suspensions in concentrations ranging from 0·25 to 1%. Benzalkonium chloride was added in a concentration of 0·01% as a preservative. Subsequently, a series of ointments was prepared in soft paraffin ophthalmic base, in which the concentration of acycloguanosine ranged from 0·03 to 3%. These formulations were prepared in the Wellcome Pharmaceutical Research and Development Laboratories, Greenville, NC, USA.

Idoxuridine was tested in the form of Kerecid, a 0·5% ophthalmic ointment marketed by Smith, Kline and French Laboratories, Welwyn Garden City, Herts, England.

Vidarabine (ara-A) was used in the form of Vira-A, a 3% ophthalmic ointment marketed by Parke, Davis & Co., Ann Arbor, Michigan, USA.

Intravenous preparation

Ampoules containing 500 mg of acycloguanosine in the form of the freeze-dried sodium salt were supplied by the Wellcome Pharmaceutical Research and Development Laboratories, Greenville, NC, USA. The material was re-dissolved by the addition of 25 ml of sterile distilled water. A fresh ampoule was reconstituted for each series of injections.

Animals

The experiments were carried out on New Zealand white and half-lop rabbits weighing about 2·25 kg. They were obtained from Ranch Rabbits, Crawley Down, Sussex, England. The half-lop rabbits were used in experiments requiring repeated intravenous injections.

Virus

The work was carried out with the PH8 strain of type 1 herpes simplex virus, which was obtained from Mr J. McGill, Southampton Eye Hospital, Southampton, England. The virus was grown in cultures of VERO cells. At the height of infection the cultures were disrupted by sonication. The stock suspension of virus thus obtained was placed in ampoules in volumes of 1 ml and stored at -70°C. For the infection of rabbits an ampoule was thawed and diluted to a concentration of virus of around 10^6 plaque-forming units per millilitre. The same stock of virus was used for all the experiments described.

Method of infection

Both eyes of a rabbit were infected by a modification of the method of Jones *et al.* (1968) described by Collins and Bauer (1977). The virus was inserted into the corneal epithelium at 8 sites by trephination with a glass capillary tube. The same concentration of virus was used for all insertions. After 3 days the developing lesions were visualised with sodium fluorescein (Fluorets, Smith & Nephew Pharmaceuticals Ltd., Welwyn Garden City, Herts, England). The extent of the ulceration was recorded by drawings on a protocol sheet, and the degree of infection was quantitated by the numerical scoring method of Corwin *et al.* (1963).

Treatment

In all cases treatment was begun on the 3rd day of infection. A drop of acycloguanosine solution was applied to 1 eye 5 times a day at intervals of 2 hours. The other eye was left untreated. Ointments were applied to 1 eye with a similar treatment schedule. The amount of ointment used at each dosing ranged in length from 10 to 15 mm and weighed 20 to 30 mg. The other eye was treated with ophthalmic ointment base for control purposes. Treatment was carried out for 4 days. The extent of infection in both eyes was recorded daily, and the experiments were terminated on the 7th day of infection, at which time the result of treatment was assessed.

The sodium salt of acycloguanosine was injected into the marginal ear vein in a dose of 50 mg/kg. The injections were given twice daily at 9 a.m. and 4 p.m. for 4 days. The result was assessed on the 7th day of infection in comparison with a control group of infected animals which did not receive treatment.

Experimental design

Preliminary experiments to establish the antiviral activity of acycloguanosine supensions were carried out under open conditions without the use of a placebo. Comparison of acycloguanosine ointments with the other antiviral preparations was carried out by a double-blind procedure with ophthalmic ointment base as placebo, in which the observer was unaware of the treatment given.

Determination of acycloguanosine levels in tear fluid

For the determination of acycloguanosine levels a biological method based on the plaque inhibition test (Herrmann, 1961) was used. Discs of filter paper 6 mm in diameter were placed in the lower fornix of each eye of an animal treated with acycloguanosine and left until saturated with tear fluid. Monolayers of VERO cells in 60-mm plates were infected with type 1 herpes simplex virus and covered with an agarose overlay. A disc was placed in the centre of the overlay and the plates were incubated to allow plaques to develop. The cultures were then fixed with 10% formaldehyde in phosphate-buffered saline for 1 hour. The overlay was removed and the plaques were visualised by staining the cell sheet with 0·5% methyl violet in 20% methanol. The diameter of the zone of inhibition of plaque formation was measured in millimetres. The concentration of acycloguanosine was then read off from a standard curve obtained with discs dipped in solutions of acycloguanosine of known micromolarity. The diameter of the zone of inhibition had a linear regression on the logarithm of the concentration over the range from 5 to 500 μM.

PRECLINICAL TOXICITY STUDIES

Animals

Evaluation of eye irritancy and ocular toxicity was carried out in New Zealand white rabbits (Franklin Farms, Wake Forest, NC, USA), pure-bred beagle dogs (Marshall Research Animals, North Rose, NY, USA), Sprague-Dawley rats (Charles River Laboratories, Wilmington, Mass., USA) and female CD-1 mice (Charles River Laboratories).

Examination of the eye

The eyes of all animals were evaluated by indirect ophthalmoscopy, biomicroscopy, and histological examination except where otherwise indicated. Before examination the pupils were dilated with 1% tropicamide solution (1% Mydriacyl, Alcon Laboratories Inc., Fort Worth, Texas, USA). In eye irritancy studies the cornea was stained with fluorescein (Fluor-I-strip, Ayerst Laboratories Inc., New York, NY, USA). At the end of the test period the animals were killed and the eyes were removed and fixed in Zenker's acetic acid solution, and processed essentially in accordance with the methods described by Levy *et al.* (1965). Full anteroposterior sections approximately 7 μm thick were taken through the optic nerve head, stained with haematoxylin-eosin, and examined by conventional light microscopy.

STUDIES

Eye irritancy study in rabbits

Groups of 8 rabbits were treated with 1, 3, and 6% ointments of acycloguanosine in white petrolatum vehicle. Control groups were dosed with vehicle or balanced saline. The test materials were instilled into the conjunctival sac of 1 eye of each rabbit 5 times daily at 90-minute intervals for 21 consecutive days. The untreated eye served as an additional control. The condition of the eyes was assessed numerically by the method of Draize (1959) 5 days and 1 day before beginning treatment, and on 3 rabbits of each group on treatment days 1, 2, 4, 7, 14, and 21. Examination with the biomicroscope and ophthalmoscope was carried out 7 days before treatment, on the last day of the treatment period, and finally 22 days later. Five rabbits in each group were killed at the end of the 21-day dosing period and the remaining 3 per group 24 days later. Both eyes of each animal were removed and examined histologically.

Intravenous study in dogs

Groups of 8 beagle dogs were given intravenous injections of the sodium salt of acycloguanosine in doses of 10, 20, 25, and 50 mg/kg twice daily for 30 consecutive days. It was prepared as an isotonic solution in sterile 0·4% sodium chloride solution. Two control groups of 8 dogs were dosed with 0·9% sodium chloride solution. The interval between doses was about 6 hours. The eyes were examined before and at the end of dosing. Histological examination was carried out on the eyes of all dogs except for those in the lowest dosage group.

Intravenous study in rats

Groups of 15 male and 15 female rats were given single daily intravenous injections into the tail vein of the sodium salt of acycloguanosine in doses of 20, 40, and 80 mg/kg for 21 days. A control group was treated similarly with 0·9% sodium chloride solution. Examination of the eye was carried out on all animals before dosing and on 10 males and 10 females of each group on the 16th day of dosing. Histological examination was carried out on both eyes of all rats in the highest dosage group and of all animals in the control group.

Oral study in mice

Groups of 38 male and 38 female mice were given acycloguanosine in 0·25% agar by stomach tube in daily doses of 50, 150, and 450 mg/kg for 33 days. A control group was given agar alone. Histological examination was carried out on 10 males and 10 females randomly chosen from the top dosage group and the controls. The eyes were not examined by other methods.

The opportunity was taken to obtain additional data on ocular toxicity in animals used for the teratology studies described below.

Teratology study in rats

Groups of 21 to 25 pregnant rats were given acycloguanosine subcutaneously in doses of 6, 12·5, and 25 mg/kg twice daily from the 6th to the 15th days of gestation inclusive. Controls were given 0·9% sodium chloride solution. The eyes of 8 rats in the control and highest dosage groups and 11 each from the other 2 dosage groups were examined before and after dosing. On the 20th day of gestation the same animals were killed and the eyes were examined histologically.

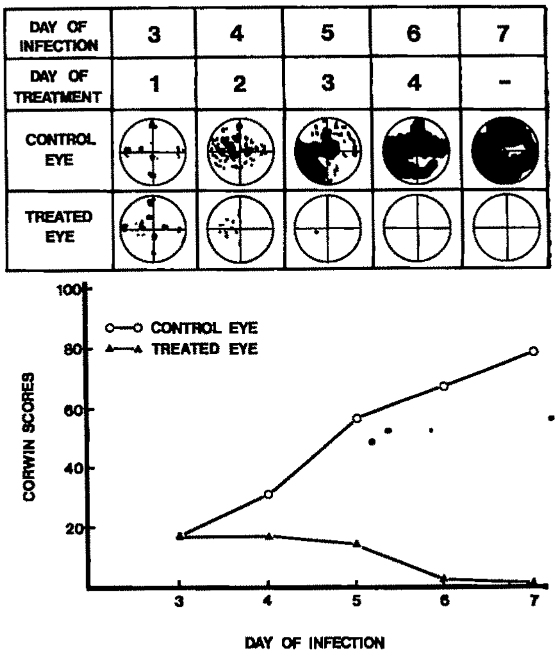

Fig. 1 *Completed protocol form of a rabbit treated with 1% acycloguanosine eye-drops. Shaded areas indicate corneal ulceration*

Teratology study in rabbits

Groups of 16 to 18 pregnant rabbits were treated from the 6th to the 18th days of gestation inclusive with the same dose levels used in the rat study. The eyes were examined before treatment and on the 29th day of gestation. The animals in the control and highest dosage groups were killed on the 29th day and the eyes were examined histologically.

In a repetition of the study carried out for the purpose of increasing the number of litters available for examination observations of the eyes were limited to visual examination.

Results

ACYCLOGUANOSINE EYE DROPS

In preliminary experiments to evaluate antiviral activity aqueous suspensions of acycloguanosine were tested in 10 rabbits. Cure was not always obtained with the 0·25 and 0·5% suspensions over the 4-day period of treatment, but a satisfactory effect was obtained with the 1% suspension. The results of such an experiment are shown in Fig. 1,

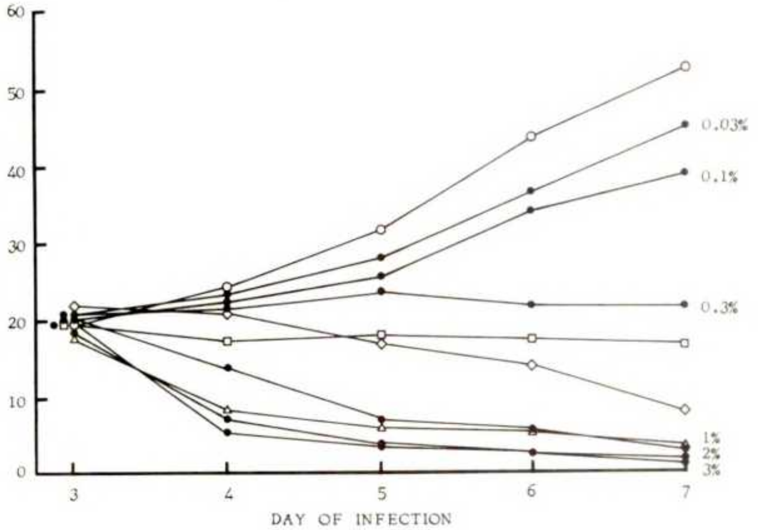

Fig. 2 *Effects of treatment with a range of acycloguanosine ointments, Vira-A, trifluorothymidine, and Kerecid on herpes simplex keratitis.* ● *Acycloguanosine.* □ *Vira-A.* ◇ *Trifluorothymidine.* △ *Kerecid.* ○ *Control*

which illustrates the correspondence between the extent of the corneal lesions and the graphs of the Corwin scores. Healing is complete by the day after the termination of treatment and the score has fallen to zero, whereas in the control eye the ulceration has involved the greater part of the cornea and the score is still increasing.

ACYCLOGUANOSINE OPHTHALMIC OINTMENTS

In a similar dose-ranging study ophthalmic ointments containing acycloguanosine in concentrations ranging from 0·03 to 3·0% were tested in a total of 60 rabbits, 10 rabbits being used for each preparation. The mean Corwin scores for each group of 10 are shown in Fig. 2. The 0·03% ointment had a perceptible effect in retarding the course of infection. This inhibitory effect increased with rising concentration, and with the 1% preparation cure was practically complete by the 4th day of treatment. The 2 and 3% ointments were both somewhat more effective, giving the maximum curative effect with the treatment regimen employed.

COMPARISON OF ACYCLOGUANOSINE WITH KERECID, VIRA-A, AND TRIFLUOROTHYMIDINE

In similar experiments Kerecid and Vira-A were each tested in 10 rabbits and trifluorothymidine in 8. The graphs of mean Corwin scores for each preparation are included in Fig. 2. From this it will be seen that cure by the 4th day of treatment was obtained only with acycloguanosine and Kerecid. Treatment with trifluorothymidine prevented the further extension of the ulceration, but the lesions were considerably slower in clearing up. Vira-A was less effective still.

ACYCLOGUANOSINE SODIUM SALT

In an investigation of the antiviral effect of acycloguanosine when administered by the intravenous route in the form of its sodium salt 6 rabbits were infected with type 1 herpes simplex virus in the usual way. Three were treated with the sodium salt by the schedule given in the Methods section, and the other 3 were left untreated as controls. The individual Corwin scores of the 6 rabbits are shown in Fig. 3. Each point represents the mean score for the 2 eyes of 1 animal. Arrest of the infection is evident on the 2nd day of treatment. After the end of treatment on the 7th day of infection a few punctate areas staining with fluorescein could still be observed. The treated animals were therefore kept for another 3 days and re-examined. The corneas were completely healed with no sign of relapse of the infection. The animals were kept for 12 months and examined at weekly intervals. No evidence of recurrence was observed.

DETERMINATION OF LEVELS OF ACYCLOGUANOSINE IN THE TEAR FLUID

The levels of acycloguanosine in the tear fluid of a rabbit after a single intravenous dose of 100 mg/kg are shown in Table 3. The level at 60 minutes is 100 times the 100% inhibitory concentration as determined by the plaque reduction method in VERO cells. Although the dose was higher than that used in the therapeutic experiment, the cure obtained with intravenous injections of 50 mg/kg may be assumed to be due to the presence of acycloguanosine in the tear fluid.

Intravenous injection was selected for the purpose of confirming that herpes simplex keratitis could be

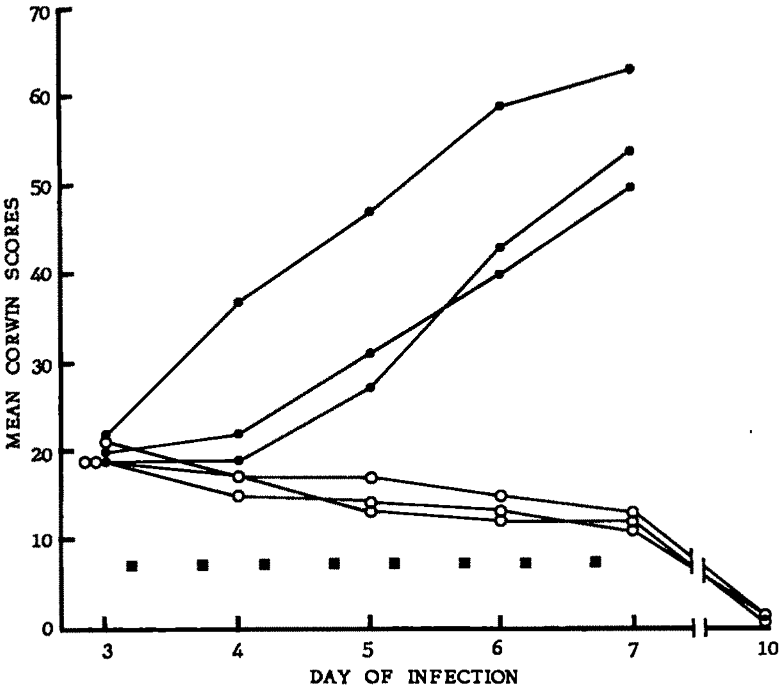

Fig. 3 *Effect of treatment of herpes simplex keratitis with intravenous injections of acycloguanosine sodium salt.*
● *Control.* ○ *Treated.*
■ *Injection given*

treated successfully by a systemic route. A more practical route in clinical practice would be administration by mouth. A rabbit was therefore given 100 mg/kg of the sodium salt of acycloguanosine by mouth, and the levels in the tear fluid were determined at intervals up to 240 minutes after administration. The results are given in Table 3. It will be seen that effective levels were present at 30 minutes, and acycloguanosine was still present at 40 times the 100% inhibitory concentration after 4 hours.

TOXICITY OF ACYCLOGUANOSINE FOR THE EYE ON TOPICAL ADMINISTRATION

In the eye irritancy study no signs of irritation occurred in rabbits treated with balanced saline. Rabbits treated with the vehicle and the ointment preparations had minimal signs of irritation which were limited to the conjunctiva and seen only during the dosing period. These signs usually appeared at the end of the dosing day and had disappeared by the following morning. The mean Draize scores for rabbits treated with the vehicle and the 1% ointment were similar. Animals treated with higher concentrations of acycloguanosine had only slightly higher scores. None of the methods of examination revealed any significant potential for ocular toxicity.

Table 3 *Levels of acycloguanosine in the tear fluid after systemic administration*

		Time (minutes)					
Dose (mg/kg)	*Route*	15	30	40	60	120	240
100	Intravenous	12*	18	29	31	ND	ND
100	Oral	ND	16	ND	14	13	12

*Concentration of acycloguanosine (μM). ND = not done

TOXICITY OF ACYCLOGUANOSINE FOR THE EYE ON PARENTERAL ADMINISTRATION

In none of the studies in which acycloguanosine was given parenterally was there ophthalmological or histological evidence of an effect on the eye. Corneal opacification was observed in 1 rabbit given the highest dose in the second teratology study. It appeared in 1 eye on the 8th day of gestation after 2 days of dosing and was bilateral by the 16th day. The opacities persisted until the animal was killed on the 29th day. Oedema of the outer third to half of the cornea was the only morphological change observed on histological examination. The aetiology was not determined, but it was not considered to be related to treatment with acycloguanosine. No similar lesions occurred in the rabbits in the first teratology study, in pregnant rats treated similarly, or in non-pregnant dogs, mice, and rats given much higher and even lethal parenteral doses of acycloguanosine for longer periods.

Discussion

The results show that satisfactory cure of herpes simplex keratitis in rabbits can be obtained with 1, 2, and 3% ointments of acycloguanosine, and with Kerecid. The 1% ointment of trifluorothymidine was less effective, and a complete cure was not obtained with Vira-A over the 4-day period of treatment. It is possible that a better result might have been obtained with Vira-A if it had been given over the daily 15-hour dosage period recommended by the manufacturers.

The finding of effective levels of acycloguanosine in the tear fluid for at least 4 hours after oral administration suggests that this route may prove effective in clinical use if adequate levels can be obtained in man. Oral administration may be the method of choice for the treatment of herpes simplex keratitis in patients with unimpaired lacrimal function, since it should be more effective in giving sustained levels in the tear film than the intermittent administration of eye drops or ointment. In this respect animal experiments have shown that acycloguanosine has an advantage over the other compounds, which are effective only when given topically.

The possibility of systemic treatment, high intrinsic activity, and lack of toxicity to the eye suggest that acycloguanosine should be of value in the treatment of herpes simplex keratitis in man.

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Experimental *Pseudomonas* keratitis in guinea-pigs: therapy of moderately severe infections

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SUMMARY We have previously shown that antibiotic therapy of experimental *Pseudomonas* keratitis was more effective in early moderate infections than in late severe infections. The purpose of this study was to determine the relative efficacies of various drugs, routes, and vehicles in the treatment of moderately severe infection. As in the late severe infections, the most consistently effective regimen was an aminoglycoside applied topically in solution. No synergistic or additive effect was observed with a combination of aminoglycoside given topically and a penicillin given intramuscularly. Topical therapy with antibiotic in ointment was less effective than topical therapy with antibiotic in solution.

We have developed a reproducible, quantitative model of experimental *Pseudomonas* keratitis in guinea-pigs. Animals are infected by intracorneal injection to ensure that all corneas receive the same inoculum. Within 24 hours all infected corneas show frank keratitis. Results of treatment are assessed objectively by determining the number of bacteria surviving in the cornea (Davis and Chandler, 1975; Davis *et al.*, 1977; Davis *et al.*, 1978).

Efficacy of treatment of experimental *Pseudomonas* keratitis in guinea-pigs was enhanced by beginning therapy sooner after infection rather than later when a more severe infection was present. Earlier therapy was presumably more effective in part because there were fewer bacteria in the cornea (Davis *et al.*, 1978).

At 16 hours after infection in this model the number of viable bacteria in the cornea has increased from a geometric mean of 10 to a geometric mean of 48 000. An abscess is beginning to form in the cornea. After 24 hours a geometric mean of 280 000 organisms are present and abscess formation is more advanced (unpublished observations). We believe that a patient with a corneal infection may well first seek medical attention at the 16-hour stage.

Here we present results of trials in which antibiotic therapy was begun 16 hours after infection. Our purpose was to determine whether the relative efficacy of antibiotics would change when infection was less severe.

Materials and methods

These have been previously reported in detail (Davis and Chandler, 1975; Davis *et al.*, 1977; Davis *et al.*, 1978). Briefly, male Hartley strain guinea-pigs weighing 300 to 350 g were infected intracorneally with about 10 viable *Pseudomonas aeruginosa* strain 107, 110, or 113. Antibiotic therapy was begun 16 hours later. At the end of the experiments the animals were killed and the corneas were excised and ground in broth. Numbers of viable bacteria were determined by quantititative subcultures. The results were analysed statistically by analysis of variance (Snedecor and Cochran, 1967). Data are presented as means and standard deviations of the numbers of viable bacteria in common logarithms (base 10). The mean of numbers expressed in common logarithms is equivalent to the geometric mean. Analysis of data in this way dampens the effect of single extreme values.

Antibiotics were obtained through the hospital pharmacy or directly from the pharmaceutical company. Parenteral formulations of aminoglycosides were diluted in sterile 0·15 M NaCl for

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Table 1 *Therapy of moderately severe experimental* Pseudomonas *keratitis in guinea-pigs**

Treatment	*Corneal colony counts*		*P*
	Mean ± *SD*	(*N*)	
0·15 M NaCl	6·18±0·43	(6)	
Tobramycin 20 mg/ml, topical	1·73±0·47	(6)	
Gentamicin 20 mg/ml, topical	1·73±0·48	(6)	>0·1
Polymyxin B, neomycin, gramicidin ophthalmic solution	1·46±0·42	(6)	<0·005
Polymyxin B, bacitracin, neomycin ophthalmic ointment	5·43±0·26	(6)	
Ticarcillin 100 mg/kg IM every 90 min	3·91±0·56	(6)	<0·05
Carbenicillin 200 mg/kg IM every 90 min	4·56±0·54	(6)	
Tobramycin 20 mg/ml topical, and ticarcillin 100 mg/kg IM every 90 min	1·51±0·87	(6)	

*Animals were infected intracorneally and treatment was begun 16 hours later. Topical treatment was given as 2 drops every 30 minutes. Ointment was applied every 2 hours. Treatment was given for 16 hours, and then all animals were killed.

Table 2 *Therapy of moderately severe experimental* Pseudomonas *keratitis**

Treatment	*Corneal colony counts*		*P*
	Mean ± *SD*	(*N*)	
0·15 M NaCl	6·07±0·89	(6)	
Tobramycin 20 mg/ml, topical	0·70±0·78	(6)	
Gentamicin 20 mg/ml, topical	0·17±0·41	(6)	
Amikacin 20 mg/ml, topical	0·79±0·88	(6)	>0·1
Polymyxin B, neomycin, gramicidin ophthalmic solution, topical	1·19±1·99	(6)	<0·005
Polymyxin B, bacitracin, and neomycin ophthalmic ointment, topical	4·06±1·50	(6)	
Ticarcillin 100 mg/kg IM	1·85±1·33	(6)	
Ticarcillin 100 mg/kg IM, and tobramycin 20 mg/ml, topical	0·33±0·52	(6)	

*Therapy was begun 16 hours after infection and was given continuously for 24 hours. Topical solutions were given 2 drops every 30 minutes. Ointment was applied topically every 2 hours. Ticarcillin was given IM every 90 minutes.

topical use. An ophthalmic solution of polymyxin B 5000 units/ml, neomycin 1·75 mg/ml, and gramicidin 0·025 mg/ml (Neosporin), and an ophthalmic ointment of polymyxin B 5000 units/g, bacitracin 400 units/g, and neomycin 3·5 mg/g (Neosporin) were used topically as formulated.

The strains of *Pseudomonas* were susceptible to the antibiotics used by standard in-vitro tests (Davis *et al.*, 1977).

Results

For the trial presented in Table 1 animals were infected intracorneally, and treatment was begun 16 hours later. Topical therapy with antibiotics was more effective than therapy with saline ($P<0·005$). Tobramycin 20 mg/ml, gentamicin 20 mg/ml, and a topical solution of polymyxin B, neomycin, and gramicidin were equally effective. Ointment containing the polymyxin B, bacitracin, and neomycin was significantly less effective than the topical solutions. Parenteral therapy with ticarcillin and carbenicillin was more effective than saline but less effective than topical therapy with antibiotic solutions ($P<0·005$). Parenteral therapy with ticarcillin did not enhance the efficacy of topical therapy with tobramycin 20 mg/ml ($P>0·1$).

In the trial shown in Table 2 therapy was begun

Table 3 *Topical therapy trials of moderately severe experimental keratitis in guinea-pigs infected with 3 strains of* Pseudomonas aeruginosa*

Pseudomonas strain	*Treatment*	*Corneal colony counts*		*P*
		Mean ± SD	*(N)*	
107	0·15 M NaCl	6·21±0·17	(6)	<0·005
	Tobramycin 20 mg/ml	1·38±0·74	(6)	
	Polymyxin B, neomycin and gramicidin	5·00±0·63	(6)	
110	0·15 M NaCl	4·55±1·82	(4)	<0·005
	Tobramycin 20 mg/ml	1·06±0·64	(5)	
	Polymyxin B, neomycin, and gramicidin	1·87±2·56	(5)	
113	0·15 M NaCl	4·73±1·00	(6)	<0·005
	Tobramycin 20 mg/ml	1·62±0·94	(6)	
	Polymyxin B, neomycin and gramicidin	2·95±0·87	(6)	

*Topical therapy of 2 drops every 30 minutes was begun 16 hours after infection and was given for 48 hours.

16 hours after infection and was continued for 24 hours. All antibiotic therapies were more effective than saline (P<0·005). Topical therapy with solutions of tobramycin, gentamicin, amikacin, and a solution of polymyxin B, neomycin, and gramicidin were equally effective. The ointment containing polymyxin B, bacitracin, and neomycin was significantly less effective than the solutions (P<0·005). Ticarcillin by intramuscular injection did not improve the efficacy of topical therapy with tobramycin in solution (P>0·1).

Table 3 presents results of trials on 3 strains of *Pseudomonas* with tobramycin 20 mg/ml and a solution of polymyxin B, neomycin, and gramicidin. Tobramycin was significantly better than saline with all 3 strains. The solution of polymyxin B, neomycin, and gramicidin was not more effective than saline with strain 107. Tobramycin was more effective than the solution of polymyxin B, neomycin, and gramicidin with strain 107 (P<0·005) but not with strain 110 (P>0·1) or strain 113 (P>0·05).

Discussion

In experimental keratitis in guinea-pigs antibiotic therapy was more efficacious when begun earlier than when begun later when the lesion was more severe (Davis *et al.*, 1978). Thus, therapy trials begun at 24 hours after infection constitute a more rigorous test of antibiotic therapy than trials begun at 16 hours after infection (Davis *et al.*, 1977). Trials begun at 16 hours after infection may possibly have greater clinical relevance than trials begun later, because an early abscess is beginning to form. Intuitively it seemed possible that some agents might be more effective in moderately severe lesions and less effective for the later, more severe lesions. The results presented show that this is not so.

Considering the data shown here and our previous work, we conclude that the most consistently effective therapy of experimental *Pseudomonas* keratitis in the guinea-pig is an aminoglycoside antibiotic given topically in solution. The combination of polymyxin B, neomycin, and gramicidin was significantly less effective in several trials (Davis *et al.*, 1977). We concluded previously that polymyxin B alone in solution was significantly less effective than gentamicin or tobramycin in solution (Davis *et al.*, 1977). The ointment containing polymyxin B, bacitracin, and neomycin was inferior in efficacy to solutions of antibiotic. Intramuscular therapy with penicillins was less effective than topical therapy with aminoglycoside solutions in concentrations greater than 3 mg/ml. Intramuscular therapy with carbenicillin or ticarcillin did not significantly improve results of topical therapy with an aminoglycoside. In 1 trial, tobramycin, gentamicin, and amikacin were equally effective when applied topically in equal concentrations.

In brief, the most consistently effective therapy for experimental *Pseudomonas* keratitis in guinea-pigs is a topical aminoglycoside solution in the highest concentration that can be applied with safety (Davis *et al.*, 1977; Davis *et al.*, 1978). The relative efficacy of antimicrobial agents in this model did not change regardless of whether the therapy was started 16 or 24 hours after infection.

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Survey of ophthalmic conditions in a Labrador community. I. Refractive errors

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SUMMARY Of the 745 available members of the population of Nain in Labrador 650 (87%) were screened for refractive errors and ocular disease. Refraction by retinoscopy was done in 553 and axial length measured by an optical method in 514. The results showed that the incidence of low degrees of myopia was higher in Inuit (Eskimos) and those of Mixed Inuit-Caucasian blood in the age groups 10 to 40 than in those over 40. 75% of the myopes came from 20 families in which myopia was present in 2 or more generations. Although there was no significant correlation between the refraction of parents and offspring, there were significant correlations between them for axial length. The axial lengths of the myopic eyes of the Inuit and Mixed populations were significantly longer than emmetropic and hypermetropic eyes. The younger members of the population were taller than their parents, and except in female Caucasians axial length showed a significant positive correlation with height. More myopes than emmetropes and hypermetropes achieved grade 8 or more in school. It is suggested that the increased incidence of myopia in the younger age groups might be due to environmental factors interfering with the process of emmetropisation in eyes with a genetic predisposition to myopia by virtue of inheriting a slightly longer eye. Better nutrition resulting in an increase in stature may also have had some influence.

There are now a number of reports of an increased incidence of myopia in the younger generations of North American Indians and Inuit (Eskimos) in Canada and Alaska (Young *et al.*, 1969; Cass, 1973; Boniuk, 1973; Morgan and Munro, 1973; Woodruff and Samek, 1977). Surveys of such populations have shown few cases of myopia in the older population but incidences of 30 to 80% have been found in the 15 to 35 age groups, suggesting that environmental rather than genetic factors are concerned.

Data from routine eye clinics in Nain, Labrador, suggested that there was such an excess of myopia in this population, but as this apparent excess in the younger population might have been due to sampling errors it was decided to attempt a total population survey of refractive errors and other eye conditions in Nain during a regular 6-monthly eye clinic. The resident population of Nain, which lies at latitude 56° 33′ N on the coast of Labrador, consisted of 419 Inuit, 253 mixed Inuit and Caucasian, 89 Caucasian, and 12 of other ethnic origin making a total of 773. 28 Inuit were away seal hunting and were not available for examination.

Under the auspices of the International Grenfell Association and with the help and support of the Canadian National Institute for the Blind a team of ophthalmologists and a refracting optician visited Nain for 2 weeks in October 1977. The examinations were held in the Nursing Station, and in addition to the collection of data for the survey any necessary ophthalmic treatment was also provided.

Patients and methods

Those willing to attend for examination were given appointments, usually on a family basis, and a data sheet was made out for each person. The name, age, sex, height, and weight were completed by the nurse, and the people were then seen by one of the ophthalmologists, who performed keratometry and axial length measurements and also examined the optic disc for cupping and the presence of crescents round the disc. They were then refracted by the optician and finally examined on a Haag-Streit 900 slit-lamp microscope. In everyone over 40, and

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Table 1 *Age, sex, and race of Nain population surveyed (number not seen in parentheses)*

Year of birth	*Inuit*		*Mixed*		*Caucasian*		*Other*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
1967–77	49 (5)	61 (9)	46 (7)	45 (5)	6	14 (2)	3	0
1957–66	53 (12)	31 (3)	32 (3)	23 (1)	3 (3)	8 (1)	2	2
1947–56	15 (6)	23 (6)	23 (3)	14	5 (3)	5	0	3
1937–46	15 (4)	15 (2)	6 (1)	8 (1)	12 (1)	4 (1)	0	0
1927–36	14 (6)	14 (5)	7	6	5	4	0	0
1917–26	8 (2)	6 (1)	9	6	4	1	0	1
Pre-1917	14	10	3	4	4	3	0	1
Total	168 (35)	160 (26)	126 (14)	106 (7)	39 (7)	39 (4)	5	7

when there was a family history of glaucoma, the anterior chamber depth was measured with the Haag-Streit attachment, and applanation tonometry was performed. In selected cases gonioscopy was also carried out. The questionnaire about place of longest residence, schooling, occupation, and snow blindness was then completed.

It was originally planned to attempt an assessment of diet for each individual, but after advice from a dietician it was concluded that the results would be too unreliable to have any value. We did, however, obtain information from the manager of the earlier Hudson Bay store as to the type of store goods which had been available to the population over the last 35 years.

KERATOMETRY AND AXIAL LENGTH

The horizontal radius of curvature of each eye was measured with the keratometry attachment to the Diag slit-lamp microscope (Clement Clarke International). Axial length was estimated by a modification of an optical method previously described (Perkins *et al.*, 1976). The method consists of measuring the distance between the corneal image of 2 illuminated slits positioned so that the eye rotates through an angle of 40 degrees in looking from one slit to the other. In the original method the corneal reflexes were photographed, and subsequently the distance between the 2 reflexes was measured on the film. For survey purposes the camera was replaced by a measuring microscope with an illuminated scale in the eyepiece. The position of the corneal image within the eye was taken as a point half the radius of curvature of the cornea along the optic axis. A comparison of this method with ultrasonography (Grey *et al.*, 1977) had shown that the anterior radius of rotation of the globe was greater than the posterior radius by approximately half the radius of curvature of the cornea and allowance for this was made in the calculation of axial length. The results suggest that this empirical correction may be too large, and emphasis will be placed on comparisons of the lengths obtained rather than the absolute values.

REFRACTION

The persons were refracted by means of retinoscopy and when possible subjective testing. We performed retinoscopy without cycloplegia but taking care that fixation was maintained on an object 6 m away. Cycloplegia was used only in a small number of children, particularly when cover testing (done routinely) suggested a squint.

EXTERNAL EXAMINATION

Particular attention was paid to the presence or absence of epiblepharon, pinguecula, pterygium, corneal scarring, and spheroidal degeneration, and the results of this part of the survey will be reported later.

Results

A total of 650 members of the population were seen, representing 87% of those in residence. This included a number of children who were in a residential school at Northwest River and were examined in the Hospital at Northwest River before the team went to Nain. The age, sex, and racial structure of the population is shown in Table 1, and the figures in brackets indicate those members of the population who were not screened. Fig. 1 shows the age distribution of the population. From Table 1 it can be seen that the sample screened is representative of the total population except for a deficit of young male Inuits.

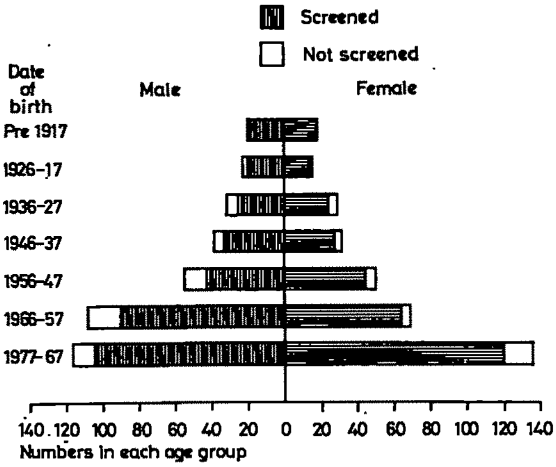

Fig. 1 *Age and sex distribution of the population of Nain in 1977, combining the figures for the racial groups*

Table 2 *Incidence of refractive errors*

Refraction	*Inuit*	*Mixed*	*Caucasian*
−5·00	4	1	0
−4·50	1	0	0
−4·00	1	0	0
−3·50	0	3	0
−3·00	0	1	1
−2·50	7	3	1
−2·00	4	4	1
−1·50	3	5	1
−1·00	4	6	4
−0·50	12	17	2
−0·25	14	11	5
Plano	27	26	9
+0·25	55	31	17
+0·50	46	25	6
+1·00	60	49	11
+1·50	17	11	7
+2·00	8	3	3
+2·50	3	3	0
+3·00	9	0	1
+3·50	1	0	1
+4·00	0	0	1
+4·50	1	0	0
+5·00	4	1	1
Total	281	200	72

REFRACTIVE ERRORS

The distribution of refractions of all right eyes (expressed as equivalent spheres) is shown in Table 2. The general pattern is similar in all 3 racial groups, and low degrees of hypermetropia account for approximately 60% of refractive errors in each group. The great majority of the myopes had low refractive errors (less than −3·0 D) and the incidence was higher in females (57%) than in males (43%). The refractions divided into myopia (⩾ −0·25 D), emmetropia (±0·25 D), and hypermetropia (⩾0·25 D) for the 3 ethnic groups and the total population are shown in Table 3. There is a higher percentage of myopes in the Mixed group and the difference in percentage between the Mixed and Inuit is just significant ($\chi^2=4{\cdot}18$, $0{\cdot}05 > P > 0{\cdot}02$).

Figures for the distribution of refractive errors in the floating population (Caucasian nurses, technicians, teachers, etc.) are given separately in Table 3, and it is interesting to note that 50% were myopic. The floating population have not been included in any subsequent analysis.

The distribution of myopia (⩾ −0·25 D) by date of birth and race is shown in Table 4 and Fig. 2. The incidence rises with age, reaching peaks in those born during 1942–56, that is, those aged between 20 and 35 at the time of screening. The percentage incidence then drops sharply for those born in the preceding decade (1932–41) and then rises in the Mixed and Caucasian populations. As will be discussed later, the myopia in some of the older people was found to be associated with pathological changes in the cornea or lens. In Fig. 3 the results from all 3 races have been combined, and the graph clearly shows the sharp rise in incidence of myopia in those born after 1941.

A comparison of the incidence of myopia in the total population for those born between 1942 and 1961 (thus excluding children of 16 whose refraction may continue to change with growth) and those born before 1942 is shown in Table 5, and the difference between the age groups is statistically significant ($\chi^2=6{\cdot}3$, $0{\cdot}02 > P > 0{\cdot}01$).

Table 6 shows a similar comparison for the 3

Table 3 *Distribution of refractive errors by racial group*

	Myopia ⩾*0·25 D*	*Emmetropia* < ±*0·25 D*	*Hypermetropia* ⩾+*0·25 D*
Inuit	50 (17·8%)	27 (9·6%)	204 (72·6%)
Mixed	51 (25·5%)	26 (13·0%)	123 (61·5%)
Caucasian	15 (20·8%)	9 (12·5%)	48 (66·7%)
Totals	116 (21·0%)	62 (11·2%)	375 (67·8%)
Floating population	10 (50·0%)	2 (10·0%)	8 (40·0%)

races separately, but only in the Inuit is there a significant difference in the incidence of myopia in the 2 age groups.

The fact that some of the older population were myopic raises the question whether genetic factors could be involved. Fortunately a recent census of the population was available, and from this and the help of the nursing staff and interpreters it was possible to construct family trees which included most of the myopes. From this, it transpired that 76 myopes came from 20 families in which myopia was present in 2 or more generations; in 11 there was a more doubtful family history, and there was no family history in 16.

According to Sorsby and Benjamin (1973) the ocular components which are genetically determined are axial length and corneal curvature over

Table 4 *Incidence of myopia (>0·25 D) by age and racial group*

Date of birth	Number and % of myopic eyes					
	Inuit		Mixed		Caucasian	
1972–77	0	0·0%	1	11·1%	1	16·7%
1967–71	3	5·1%	9	17·3%	1	12·5%
1962–66	11	20·0%	7	24·1%	2	28·6%
1957–61	9	31·0%	8	32·0%	0	0·0%
1952–56	8	40·0%	6	28·6%	3	42·9%
1947–51	6	35·3%	5	31·3%	1	25·0%
1942–46	5	33·3%	5	62·5%	2	18·2%
1937–41	1	6·7%	1	16·7%	0	0·0%
1932–36	3	16·7%	0	0·0%	0	0·0%
1927–31	1	11·1%	0	0·0%	2	50·0%
1922–26	1	11·1%	4	36·4%	1	33·3%
1917–21	0	0·0%	2	50·0%	1	50·0%
pre-1917	2	11·1%	3	50·0%	1	16·7%

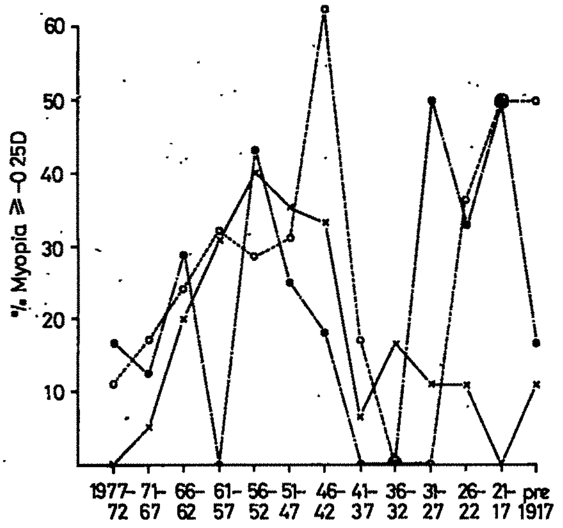

Fig. 2 *Percentage of each age group with myopia equal to or greater than -0·25 dioptres, according to racial origin. Inuit X—X. Mixed ○ --- ○. Caucasian ●—·—●*

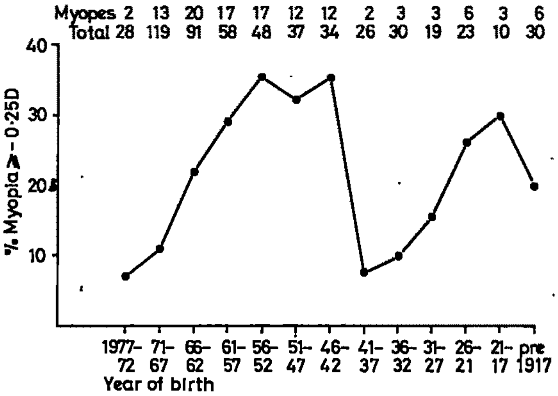

Fig. 3 *Percentage of population in each 5-year age group with myopia equal to or greater than -0·25 dioptres, combining the results for the racial groups*

Table 5 *Incidence of myopia in total population over the age of 16 years*

Date of birth	No. of myopes	No. of non-myopes	% myopia
1942–61	58	177	24·7%
Pre-1942	23	138	16·7%

(χ^2 = 6·3, 0·02>P>0·01)

Table 6 *Incidence of myopia by racial group over the age of 16 years*

Race	Date of birth	No. of myopes	No. of non-myopes	% myopia
Inuit	1942–61	28*	81	25·7%
	Pre-1942	8	73	9·9%
Mixed	1942–61	24	70	25·5%
	Pre-1942	10	40	20·0%
Caucasian	1942–61	6	26	18·8%
	Pre-1942	5	25	20·0%

(*χ^2 = 7·56, P<0·01)

the range of ±4·00 D, and these findings were confirmed in a study of Greenland Eskimos by Alsbirk (1977). We therefore calculated the correlation coefficients for refraction and axial length for 76 families on which data was available. The results are shown in Table 7, and it can be seen that there is no correlation between the parents and children for refraction but there are significant correlations for axial length. Proof of a purely genetic determination theoretically requires a correlation coefficient of 0·5, and, although we found no correlations as high as this, the figures for fathers and daughters, and fathers and sons are very suggestive of a genetic component in axial length.

AXIAL LENGTH

As previously stated, the calculation of axial length included an empirical factor which in a previous series of measurements on Caucasian eyes seemed to give a better correlation between the results of the optical method and ultrasonography. The results shown below suggest that the calculated values are too low, and emphasis should be placed on comparisons rather than actual values.

The mean axial lengths for right eyes for which satisfactory readings were obtainable are given in Table 8 for the 3 racial groups.

There are significant differences between the means for the 3 racial groups, the Caucasians having the longest and the Inuit the shortest mean axial length. These results might be biased owing to the larger number of young people in the Inuit and Mixed groups, but a comparison between the mean axial length of the eyes of Inuit and Mixed subjects over the age of 20 (Table 9) shows that they are significantly shorter than Caucasian eyes (P < 0·046).

There are also very significant differences in the mean axial length for different refractive states in the Inuit and Mixed group. The myopic eyes have the largest axial length (Table 10).

This was not so for the Caucasians, in whom the emmetropes had the longest mean axial length of 22·67 mm and the hypermetropes a mean of 22·36 mm. The greater length of the emmetropic eyes could have been due to the preponderance (17 to 2) of male eyes in this group.

BODY HEIGHT

As would be expected, there was a significant correlation between axial length and age in the first 2 decades. We were interested, however, in any possible correlation between axial length and body build, as we had gained the impression that the older Inuit and Mixed who were rather short also had short eyes. Analysis showed that this impression was correct not only for both male and female adults of Inuit and Mixed subjects but also for male Caucasians as shown below (Table 11). The mean

Table 7 *Correlation of refraction and axial length between parents and children*

	Refraction		*Axial length*	
	r	*P*	*r*	*P*
Fathers and sons	−0·074	0·24	0·317	<0·001
Fathers and daughters	0·059	0·33	0·357	<0·004
Mothers and sons	0·007	0·47	0·027	0·40
Mothers and daughters	−0·054	0·32	0·197	<0·044
Parents and children	−0·014	0·40	0·196	<0·001

Table 8 *Mean axial lengths of all right eyes by racial groups*

Race	*No.*	*Mean AL*	*Standard deviation*
Inuit	258	21·87 mm	±0·9905
Mixed	188	22·26 mm	±0·9271
Caucasian	68	22·59 mm	±1·0211

Table 9 *Mean axial lengths of right eyes of Inuit and Mixed populations compared with Caucasian eyes (Subjects over the age of 20 years)*

Race	*No.*	*Mean (mm)*	*Standard deviation*
Inuit and Mixed	161	22·23	±0·9524
Caucasians	63	22·59	±1·0211

Table 10 *Mean axial lengths in different refractive states for Inuit and Mixed combined*

Refraction	*No. of eyes*	*Mean AL (mm)*	*Standard deviation*
⩾ −0·50 D	75	22·69	±0·935
±0·50 D	158	22·11	±0·899
⩾ +0·50 D	214	21·75	±0·936

Table 11 *Axial length and height*

Race	*Sex*	*Correlation coefficient*	*Significance*	*No. of eyes*
Inuit and Mixed	Males	$r = 0{\cdot}533$	P<0·001	104
Caucasian	Males	$r = 0{\cdot}415$	P<0·025	30
Inuit and Mixed	Females	$r = 0{\cdot}281$	P<0·01	97
Caucasian	Females	$r = 0{\cdot}384$	P<0·1	15

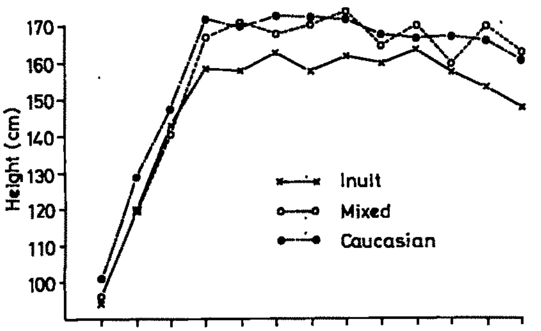

Fig. 4 *Mean heights of males, according to racial origin, for each age group*

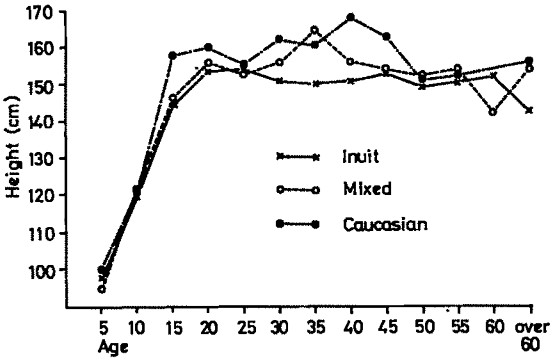

Fig. 5 *Mean heights of females, according to racial origin, for each age group*

heights for males and females of each group by age are shown in Figs. 4 and 5.

The mean height of the Inuit and Mixed population in the third and fourth decades is greater than that of those over 40 (males by 7·24 cm, females by 3·53 cm). Further analysis showed that there was a significant positive correlation between height and axial length in this population over the age of 20 (Table 11).

ASTIGMATISM

Astigmatism of more than one dioptre was found more frequently among the Inuit than the Mixed and Caucasians (Table 12).

Corneal disease (old tuberculous interstitial keratitis or other corneal scars) might have caused 6 cases in the Inuit and 2 cases in the Mixed. The astigmatism was against the rule in half the Inuit eyes and in 10 out of the 12 Mixed race eyes. The highest error was –3·00 sph –7·00 D cyl in a patient with severe corneal scarring.

Lesser degrees of astigmatism, 0·5 to 1·00 D, were also more common in the Inuit (Table 13).

SCHOOL PERFORMANCE

In view of suggestions that myopia is the result of the extra accommodative effort required in school work we compared the scholastic achievement of myopes (–0·50 D or more) with hypermetropes (+0·50 D or more) in the Inuit and Mixed races born between 1942 and 1962 (age from 15 to 35) (Table 14). From Table 14 it will be seen that the mean school grade of the Inuit is higher for myopes than hypermetropes, but this is not so for the Mixed population.

A comparison of those myopes achieving grade 8 or better with emmetropes and hypermetropes combined in the total population over the age of 15 is shown in Table 15.

Table 12 *Astigmatism over 1 D (right eyes)*

Race	*Total refractions*	*Astigmatism*	*Against the rule*	*Astigmatism*	*Mean error*
Inuit	281	32	16	11·39%	3·23 D
Mixed	200	12	10	6·00%	2·35 D
Caucasian	74	4	3	5·56%	2·00 D

Table 13 *Astigmatism 0·50 to 1·00 D*

Race	*Total refraction*	*Astigmatism*	*Against the rule*	*% Astigmatism*
Inuit	281	23	20	8·19
Mixed	200	11	3	5·5
Caucasian	74	3	2	4·05

Table 14 *Mean school grade achieved by myopes and hypermetropes aged 15 to 35*

	Inuit	*Mixed*
Myopes	7·37 (19)	8·41 (17)
Hypermetropes	6·96 (26)	8·67 (21)

Table 15 *Achievement of grade 8 by ethnic group and refraction*

Race	*Grade*	*Myopes (≥–0·50 D)*	*Other refractions*
Inuit	8	14	34
	< 8	13	93
	% 8	51·9	31·17
Mixed	8	16	46
	< 8	11	106
	% 8	59·26	34·64

It can be seen from this table that a higher proportion of myopes from both groups achieved grade 8 or better and these differences are statistically significant (for Inuit $\chi^2=6{\cdot}53$, $0{\cdot}027 > P > 0{\cdot}01$ and for the Mixed $\chi^2=8{\cdot}51$ $P < 0{\cdot}01$). These results could be biased because the older population (>35 years) in whom the incidence of myopia was lower did not have the same educational opportunities as the younger age groups and would have been unable to attend school long enough to achieve grade 8.

Discussion

One of the first problems encountered in this survey was the division of the population into ethnic groups. It is sometimes stated that there are no pure Inuit in Labrador. We believe that this is not true, as some of the people in Nain had migrated from further north and were of the same stock as the population of Baffin Island. This area of Labrador has been visited by Europeans for hundreds of years, and it is impossible to be sure that some of the people classified as Inuit did not have a few Caucasian genes. The division into Inuit, Mixed, and Caucasian was made in consultation with the interpreters and older inhabitants and may not be completely accurate. If the family history suggested that more than 1 great grandparent was Caucasian they were classified as Mixed.

Living conditions in Nain are relatively good. Housing for most families is adequate. Electricity is available, and the majority of families have a telephone and television set. There is little employment locally except for the traditional fishing and employment in the fish processing plant in the summer and hunting in the winter. This does mean, however, that natural protein is available fairly freely, although it was clear from conversations with storekeepers that a wide range of store food has become available and used over the last 30 years. Before 1942 the main foods bought from Hudson Bay Company Store comprised flour and molasses, but with the advent of the Government Store in 1946 an increasing variety of imported food provided a considerable proportion of the diet—mainly in the form of carbohydrates.

MYOPIA

The tables presented show that myopia occurs more frequently in the Inuit and Mixed population between the ages of 10 and 40 than in the older population, though the difference is not so striking as that reported from other communities—the Eskimos in Barrow, Alaska, for example (Young *et al.*, 1969). It is interesting to see that the Caucasians also showed a similar pattern in the incidence of myopia with age. They have been exposed to very similar environmental and dietetic influences as the other racial groups. In both the Mixed and Caucasian groups the incidence of myopia in the subjects over the age of 40 was rather high and prompted a closer look at the records from these individuals to see if there was any ocular pathology which could account for the myopia. This showed that 6 out of the 9 Mixed race myopes had a marked degree of Labrador keratopathy (spheroidal degeneration of the cornea) and 2 others had lesser changes. All 5 Caucasian myopes over the age of 40 had marked keratopathy and 1 also had chronic simple glaucoma. Even among the 7 Inuit myopes over the age of 40, 5 had keratopathy (1 also had cataract) and the other 2 had corneal scars from old keratitis. One of the latter had very distorted corneae with the highest myopic refractive error in the whole population (−3·00 D Sph −7·00 D cyl).

The axial lengths of the older Inuit and Mixed race eyes also suggested that the myopia was not axial in many cases. In only 7 out of 16 Inuit and Mixed was the axial length greater than the mean for emmetropic eyes.

These findings suggest that ocular pathology could account for some of the apparent myopia in the older age groups, and if these eyes with corneal lesions and/or lens changes are excluded the preponderance of myopia in the younger age groups becomes more significant.

Woodruff and Samek (1977) pointed out that the cylindrical component of the refractive error may cause the equivalent sphere to be of negative sign. Examination of the astigmatic errors in our series showed that this was only true for 6 Inuit and 7 Mixed myopes of −0·25 D or more.

Astigmatic errors were commoner among the Inuit than in the other races and were more often against the rule.

The most marked difference in the age incidence of myopia occurs between those born between 1942 and 1946 and those born in the previous decade. This means that the rise in incidence of myopia coincides with the advent of a wider choice of foodstuffs available from the Government store, which suggests a dietary influence. However, it is also probable that more children born after 1942 had better educational opportunities and more intensive schooling than those born before 1942, so that in addition to a change in diet there is the possibility of increased close work playing a part.

The attempt to compare educational achievement with refraction was based on school grades, which may not be a very satisfactory method of assessing the amount of close work done. The results did show that a higher proportion of the myopic Inuits and Mixed subjects achieved grade 8 than emmetropes and hypermetropes. There is therefore some evidence to support the contention that educational achievement is higher in myopes or alternatively that myopia is more likely in those with higher educational achievement.

Axial length measurements showed that myopic eyes were significantly longer than emmetropic and hypermetropic eyes and that irrespective of refraction the mean axial length of eyes from the 3 racial groups were significantly different, the Inuit eyes being shortest and the Caucasian eyes being longest. These differences could be due to differences in body statue. Figs. 4 and 5 show that from the age of 30 the Caucasians are on average consistently taller than the Inuits. The Mixed group heights are closer to the Caucasian population than to the Inuit.

Although many of the myopes come from families in which myopia was present in 2 or more generations there was no correlation between refraction of parents and children. There was, however, a significant correlation between parents and children with regard to axial length.

The main object of the refractive survey was to examine the incidence of myopia to see if it supported suggestions that environmental factors could be responsible. Our results support previous studies in Indian and Eskimo populations showing an increase in simple myopia in the younger age groups and confirm that the myopic eyes are associated with a longer axial length than emmetropic and hypermetropic eyes.

It is generally agreed that refractive errors are not distributed normally as are other physical features such as height and weight but show an excess of emmetropia, which is brought about by an active process. Low degrees of ametropia can be looked upon as a failure of this process to produce emmetropia, and it is certainly possible that environmental factors could be involved. The fine adjustment of refraction is probably brought about by the refractive power of the lens, and if, for example, the lens does not flatten sufficiently during the growth of the eye the final refraction will be myopic. A greater degree of adjustment will be required to produce emmetropia if the axial length (which is genetically determined) departs from a median value. If the dioptric power of the lens remains too high (? as a result of excess accommodative effort) the eye will be myopic particularly if the axial length is on the long side.

Emmetropisation will be more difficult to obtain in a longer eye and any environmental factors which impede the process will have a greater effect. It is therefore possible to reconcile genetic and environmental factors by this hypothesis, and to suggest that the increased incidence of myopia in the younger generations is brought about by an environmental factor preventing complete harmonisation of the refractive components of the eye with a genetically determined longer axial length.

From the evidence available we cannot implicate any single environmental factor. There is some evidence that attendance at school might be a factor, but at the same time as schooling became more generally available there was an undoubted change in diet, with more store foods and carbohydrate providing an appreciable proportion of total food intake.

An additional factor which should also be considered is the possibility that eye size is linked to body stature. The younger age groups who have the highest incidence of myopia tend to be taller than the older population and will also tend to have longer axial lengths because they are taller. If emmetropisation is more difficult to achieve in longer eyes then myopia will result more often in the younger age groups.

It could be that better hygiene and a higher calorie diet has resulted in the younger population growing taller than their parents, with the penalty that their eyes are longer and therefore more likely to become myopic. It could be argued, however, that the less striking excess of myopes in the Nain population compared with some other northern people is due to the fact that fishing and hunting still provides a higher proportion of protein in the diet than would be obtained in populations relying almost entirely on store food.

Woodruff and Samek (1976) found a lower incidence of myopia among the Eskimos of Belcher Island, where fish and game are more plentiful, than among more northern natives, where the protein intake is lower.

There is no evidence at the moment that the myopia in this population has resulted in any serious ocular complications. Retinal detachment is very rare among the native population of Labrador but as the risk of detachment is higher even in low myopes than in emmetropes and hypermetropes (Perkins, unpublished data) it will be interesting to see whether more cases are seen in future. No typical myopic crescents or other fundus changes suggesting myopic degeneration were seen in the population examined.

We are most grateful for all the facilities put at our disposal by the International Grenfell Association and the financial support from the E. A. Baker Fund of the Canadian National Institute for the Blind. We owe a special debt of gratitude to the nursing staff at Nain under Miss S. Ambrose. Without their hard work and excellent relations with the population such a survey would have been impossible. We are also grateful for the co-operation of the interpreters and many older members of the population for their help with genealogies and general information about conditions in Nain. Our thanks are also due to the Computer Department of the Institute of Ophthalmology for the computer analyses, and to the Department of Audiovisual Communication for the graphs.

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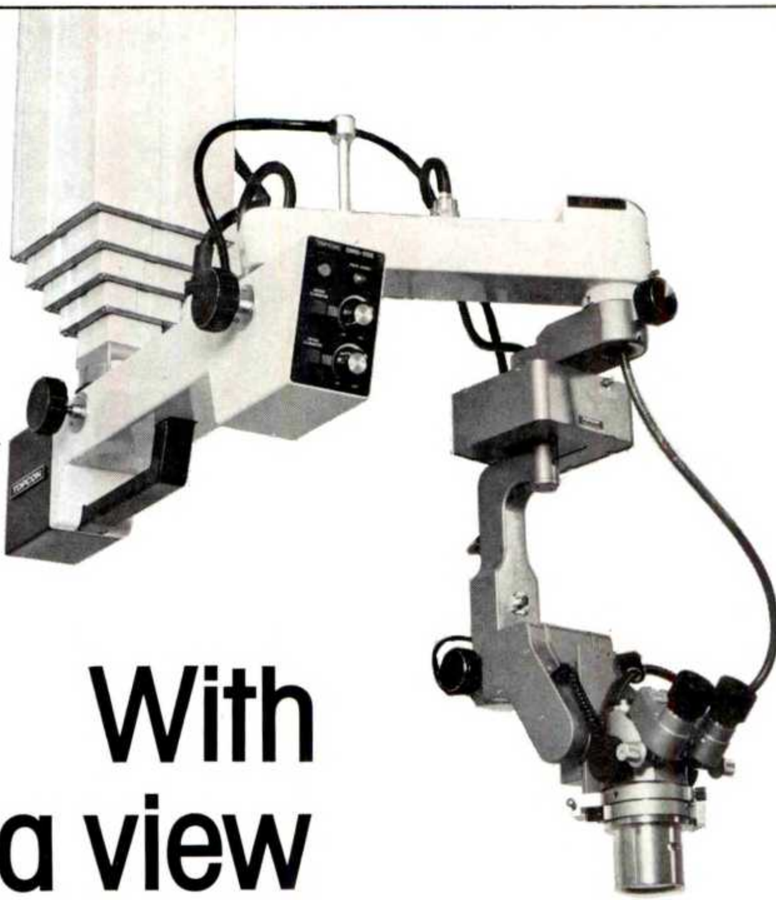

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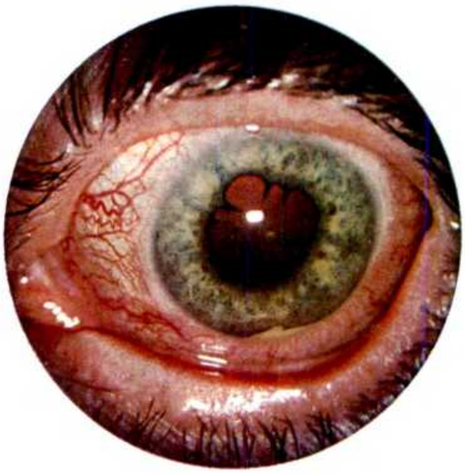

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Nocardia asteroides keratitis

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SUMMARY *Nocardia asteroides* has been reported as the cause of keratitis in only 7 cases and of other ocular disease in another 12 cases. We report a case of *N. asteroides* keratitis that presented 3 weeks after rural trauma and progressed despite trials of appropriate antibiotics. Seven weeks after the original injury a successful conjunctival flap was placed over the cornea. The morphology and the sensitivity testing of *N. asteroides* with agar dilution methods are described. Further standardisation of susceptibility testing of *N. asteroides* to antibiotics appears necessary before reliable information can be obtained for clinical use. Moreover, our case did not show the relatively benign course of other reported cases of nocardia keratitis.

Although fungal keratitis has been reported more often since the introduction of topical ocular steroid preparations (Haggerty and Zimmerman, 1958) there have been only 7 reports of *Nocardia asteroides* as the causative organism. A further 13 cases (3 bilateral) of ocular or periocular infection with this organism have also been reported.

We report a case of a progressive *N. asteroides* corneal ulcer that was unresponsive to intensive oral and topical antibiotics. One year after a Gundersen conjunctival-flap operation the eye is quiet, and a potentially useful eye has been retained.

Case report

CLINICAL SUMMARY

A 17-year-old Caucasian boy sustained injury from foreign bodies in both corneas when dirt and debris from an exploding tractor tyre peppered his eyes. He had numerous foreign bodies removed from both eyes on the day of the accident and on the following day, and received topical sulphadiazine drops. His vision and comfort gradually improved over the ensuing 3 weeks, after which his left eye became painful and visual acuity progressively diminished. He was admitted to a local hospital and given sodium sulphacetamide eyedrops for 1 week without improvement. When seen at the Johns Hopkins Hospital about 1 month after the initial injury his right eye had 20/20 vision. There was a half-thickness healed corneal laceration inferonasally, with a few foreign bodies trapped within the scar. His left eye was rather photophobic and had gross conjunctival chemosis and ciliary injection. There was a 5×5 mm one-third-thickness stromal ulcer inferonasally with irregular opaque edges (Fig. 1). Feathery projections from these edges extended for a further 1 to 2 mm at mid-stromal depth and there was a mid-stromal 'satellite' infiltrate 2 mm above the ulcer. The base of the ulcer was irregular and filled with mucus and corneal debris. The pupil was mid-dilated, and there was an intense fibrinous exudate in the anterior chamber. The lens, vitreous, and retina were normal. Vision

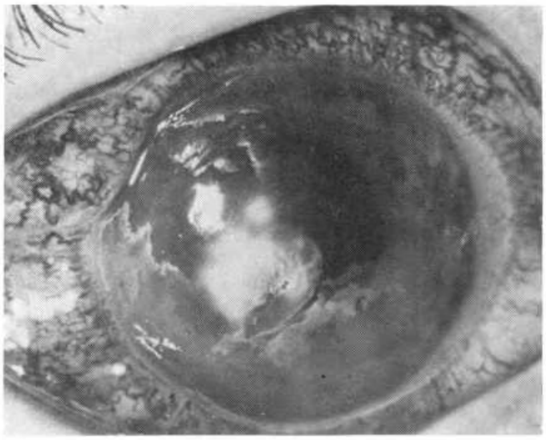

Fig. 1 Nocardia asteroides *ulcer on initial presentation at the Johns Hopkins Hospital, 4 weeks after trauma*

Address for reprints: Lawrence W. Hirst, MD, Wilmer Institute, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, Maryland 21205, USA was reduced to counting fingers at 3 ft (1 m).

Before the accident the patient had been in good health and had 20/20 vision, with surgery at the age of 3 for correction of strabismus. He had been on long-term tetracycline therapy for acne before this eye infection, but he ceased this medication on his first hospital admission after the infection. He gave a reliable history of penicillin allergy.

Smears and cultures taken on his initial admission to the community hospital were reported a week later as positive for *Nocardia asteroides* and *Alcaligenes* species. At the Johns Hopkins Hospital, 28 days later, the corneal ulcer was again scraped for smears and cultures and the patient was begun on sulphadiazine orally, 2 g every 6 hours, 30% sulphacetamide drops every 2 hours, 3% atropine drops 3 times a day, achromycin drops every 2 hours, and gentamicin drops every 2 hours. Smears taken from corneal scrapings confirmed the presence of partially acid-fast Gram-positive organisms with branching hyphae, and after 2 days cultures confirmed the presence of *N. asteroides*. Other cytological examinations were normal except for neutrophilia.

One week later the lesion and the surrounding infiltrate and anterior-chamber reaction had increased slightly. The ulcer was again scraped. No organisms were noted on smear, but cultures again grew *N. asteroides*.

Six weeks after the initial injury, despite daily irrigation of the ulcer and continuation of the intensive antibiotics, an endothelial line of keratic precipitates developed around the ulcer. This line and the ulcer size and depth showed progression over the next 2 days. A hypopyon formed, and the endothelial line extended towards the limbus (Fig. 2). Topical antibiotics were discontinued and subconjunctival gentamicin was begun, with continuation of the oral sulphadiazine.

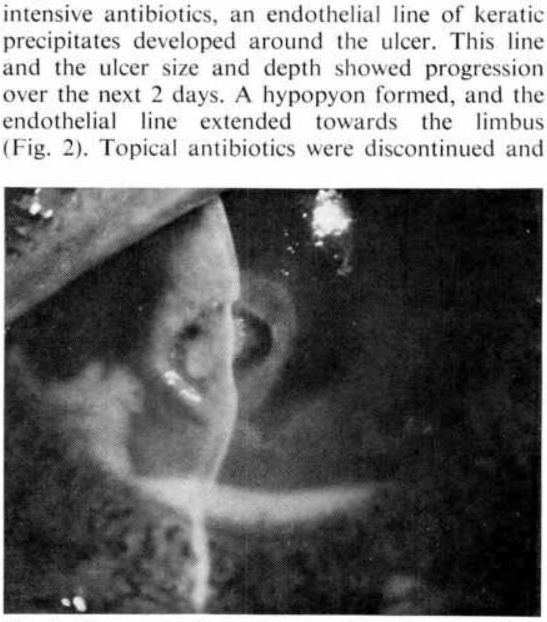

Fig. 2 *Progressive* Nocardia asteroides *ulcer, 6 weeks after trauma and 2 weeks after chemotherapy*

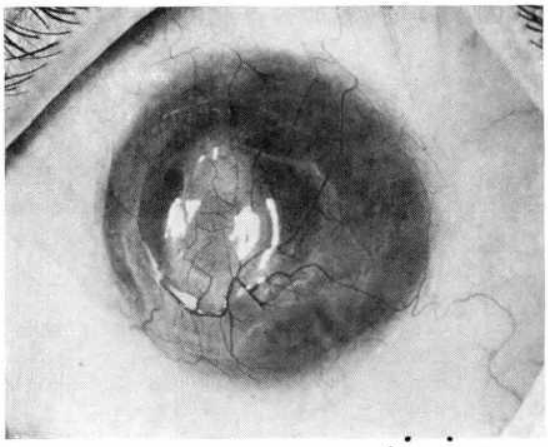

Fig. 3 Nocardia asteroides *ulcer, 1 year after successful treatment with conjunctival flap*

Over the next 5 days the ulcerated cornea thinned to less than one-quarter thickness, and the anterior-chamber reaction increased. A further scraping was performed, but no organisms were seen on smear. A conjunctival flap was placed over the entire cornea, and the eye soon became quiet. The oral sulphadiazine was continued for 2 months. One year later, the conjunctival flap had thinned and the anterior chamber, lens, and retina (posterior pole only) were visualised as normal. The intraocular pressure as measured by pneumotonometry was 15 mmHg. The nasal half of the cornea was thinned to half-thickness over an area of 5×4 mm (Fig. 3). The cornea in this area was opaque, but the eye was quiet, and the uncorrected vision was 20/200. Later a 7-mm penetrating keratoplasty was successfully performed, and no organisms were found on histological examination of the corneal specimen.

MICROBIOLOGICAL EXAMINATION

Corneal scrapings submitted soon after the patient was admitted to the Johns Hopkins Hospital revealed an aerobic growth of a pure culture of small, white, raised, dry colonies. Gram staining showed Gram-positive branching pleomorphic rods. Acid-fast staining by the Ziehl-Neelsen technique with a 3% HC1-ENH decolorisation for 10 seconds showed partially acid-fast organisms. Biochemical testing revealed no acid production from lactose and xylose, urea was decomposed but tyrosine and xanthine were not, and there was no casein hydrolysis. The organism was identified as *Nocardia asteroides*. Subsequent specimens from the corneal ulcer submitted 7 days later grew the same organisms in pure culture. Susceptibility testing of the organisms cultured at the Johns Hopkins Hospital was done by an agar dilution technique as follows. The inoculum was prepared by incubating the organism in Mueller Hinton broth for 24 hours at 35°C. After vigorous vortexing, the larger particles were allowed to settle, and the suspension was removed and standardised against a 0·5 MacFarland $BaSO_4$ standard. This suspension was diluted 1:10 and 0·01 ml was applied to the surface of the antibiotic-containing Mueller Hinton agar by means of a replicating device. All plates were incubated at 35°C for 48 hours before being examined. Inhibition was defined as no growth, 3 or fewer colonies, or the presence of a slight haze.

The minimal inhibitory concentration (MIC) results of the antibiotics tested were as follows: methicillin, greater than 16 μg/ml; penicillin, 16 μg/ml; erythromycin, greater than 2 μg/ml; clindamycin, 2 μg/ml; tetracycline, 16 μg/ml; chloramphenicol, greater than 8 μg/ml; cephalothin, greater than 32 μg/ml; ampicillin, 2 μg/ml; gentamicin, greater than 1 μg/ml.

Discussion

Nocardia are usually soil organisms, and, although they are worldwide in distribution, nocardial infections are rare, especially in the eye. The 2 most usual modes of infection are inhalation of organisms, leading to pulmonary nocardiosis; and contamination of skin wounds with soil, leading to chronic destructive mycetomas. *Nocardia asteroides* is usually an opportunistic pathogen, and pulmonary or generalised nocardiasis has become increasingly prevalent in patients with severe systemic diseases who are receiving corticosteroids or antineoplastic drugs. In addition, nocardia may rarely cause infections in other sites.

The *Nocardia* genus and the genus *Actinomyces* are members of the family Actinomycetaceae. Both genera grow as fragile branching filaments that readily fragment into bacillary rod and twig-like elements. *Nocardia* are aerobic and somewhat acid-fast, whereas *Actinomyces* are anaerobic and not acid-fast. With their filamentous growth and mycelia-like colonies, the actinomycetes have a striking resemblance to fungi. However, a number of basic biological properties establish them as bacteria (Davis *et al.*, 1969; Bach, 1975). Occasionally confusion arises in differentiating *Nocardia* from rapidly growing mycobacteria. Similarity between the genus *Mycobacterium* and the genus *Nocardia* has also been reported with respect to antigenic structure, cell-wall composition, and bacteriophage susceptibility. *Nocardia*, however, may be differentiated from mycobacteria because *Nocardia* is only partially acid-fast, it forms fragmenting mycelia and has true branching (Tsukamura, 1970). In addition, the 2 groups differ in the lipid composition of their cell walls (Davis *et al.*, 1969; Lechevalier *et al.*, 1971).

Nocardia is commonly involved in pulmonary infections, but its role in ocular infections is limited, as is evident from a search of the available literature (Table 1) (Bruce and Locatcher-Khorazo, 1942; Benedict and Iverson, 1944; Smith, 1952; Schardt *et al.*, 1956; Sigtenhorst and Gingrich, 1957; Henderson *et al.*, 1960; Gingrich, 1962; Rees, 1962; Davidson and Foerster, 1967; Meyer *et al.*, 1970; Burpee and Starke, 1971; Newmark *et al.*, 1971; Panijayanond *et al.*, 1972; Jampol *et al.*, 1973; Rogers and Johnson, 1977; Sher *et al.*, 1977). Most of the intraocular cases of nocardia infection can be traced to metastatic spread of proved primary infections elsewhere, (Davidson and Foerster, 1967; Meyer *et al.*, 1970; Burpee and Starke, 1971; Panijayanond *et al.*, 1972; Jampol *et al.*, 1973; Rogers and Johnson, 1977; Sher *et al.*, 1977) or following exogenous trauma such as cataract extraction (Meyer *et al.*, 1970). Five of the 7 previously reported nocardia infections of the cornea were preceded by trauma; 4 of these occurred in a rural setting (Schardt *et al.*, 1956; Sigtenhorst and Gingrich, 1957; Gingrich, 1962; Newmark *et al.*, 1971), and 1 was from a fishing accident (Ralph *et al.*, 1976). The trauma in all cases was considered trivial. The cases ran variable courses, but all resolved with retention of the eye and with reasonably good vision. The remaining 2 cases were associated with a keratoconjunctivitis of obscure origin (Bruce and Locatcher-Khorazo, 1942; Benedict and Iverson, 1944). One of the cases responded to therapy, but the other was deteriorating when lost to follow-up.

In only 3 of the 7 cases was the topical administration of corticosteroids (Sigtenhorst and Gingrich, 1957; Newmark *et al.*, 1971; Ralph *et al.*, 1976) a possible predisposing factor, and in these cases the drugs had been administered only briefly before the diagnosis of nocardial infection. These patients retained excellent vision. Often, however, the isolation of the causative organism may be delayed, and steroids may have been given for several months.

Our case emphasises the rural trauma, the slow initial course of the disease, the characteristic morphology of a 'fungal-type' ulcer, and the progressive nature of a nocardial infection when it is unresponsive to treatment. In this case intensive sulphonamide therapy, topically and systemically, was given in conjunction with tetracycline and gentamicin. Daily toilet of the ulcer, and 3 of the

Table 1 *Review of literature on ocular nocardiosis*

(A) *NOCARDIA KERATITIS*

Case report	*Age*	*Sex*	*Predisposing cause*	*Site of infection*	*Treatment*	*Outcome*	*Diagnostic criteria*
Bruce and Locatcher-Khorazo (1942)	50	M		Punctate kerato-conjunctivitis	Potassium iodide (*a*, *b*)*	Quiet eye	
Benedict and Iverson (1944)	23	F	? Scarlet fever	Chronic kerato-conjunctivitis	Sulphanilamide (*a*) Potassium iodide (*a*) Copper sulphate (*a*) Zinc sulphate (*a*) Metaphen (*a*) Penicillin (*a*)	4 years gradual deterioration	Positive smear and culture
Schardt *et al.* (1956)	33	M	Stone trauma on farm	Corneal ulcer	Argyrol (*a*) Cautery oxytetracline (*a*) Atropine (*a*) Achromycin (*a*, *b*)	20/80 quiet	Positive culture
Sigtenhorst and Gingrich (1957)		?	Cotton branch injury	Corneal ulcer	Sulphacetamide (*a*) Atropine (*a*) Cortisone (*a*)	Excellent	
Gingrich (1962)	53	M	Cotton plant scratch	Corneal ucler	Sulphacetamide (*a*) Penicillin (*c*) Sulphadiazine (*b*)	20/50	Positive culture
Newmark *et al.* (1971)	6	M	Dirt injury	Corneal ulcer	Oxytetracycline (*a*) Corticosteroid (*a*) Chloramphenicol (*a*) Sulphacetamide (*a*) Tetracycline (*a*) Idoxuridine (*a*) Sulphadiazine (b)	20/25	Positive culture
Ralph *et al.* (1976)	11	F	Fishline sinker abrasion	Corneal ulcer	Neomycin (*a*) Prednisone (*a*) Homatropine (*a*) Polymixin (*a*) Gentamicin (*a*) Erythromycin (*a*) Ampicillin (*d*) Sulphacetamide (*a*) Penicillin (*a*) Bacitracin (*a*)		Positive culture

*Route of administration: *a*, topical; *b*, systemic oral; *c*, systemic parenteral; *d*, periocular; *e*, intraocular

scrapings during the early course of the infection, always revealed only the presence of nocardia. The initial growth of alcaligenes was not observed on subsequent scrapings. Although it is not at all certain that long-term use of a broad-spectrum antibiotic contributed to a predisposing state, it is interesting to note that the patient was on continuous oral tetracycline therapy for acne at the time of his injury and subsequent infection, until he discontinued the tetracycline when he first entered the hospital. In-vitro testing revealed resistance of the nocardia to tetracycline.

In the face of progressive corneal thinning and increased anterior-chamber reaction despite a 3-week period of intensive chemotherapy, an operation for conjunctival flap was performed, and the oral sulphadiazine was continued for 2 months postoperatively. Therefore the dramatic response after surgery is more difficult to evaluate; it could have been due to the prolonged chemotherapy, but the lack of favourable response to sulphadiazine preoperatively makes this unlikely.

Sulphonamides, both systemic and topical, have remained the drugs of choice for ocular nocardia infections (Lerner and Baum, 1973; Ripon, 1974). Sulphadiazine and sulphamethoxazole still appear to be superior to newer antimicrobial agents for treatment of nocardiosis (Black and McNellis, 1971; Ripon, 1974). Cephaloridine and also a trimethoprim-sulphamethoxazole combination have both been used successfully in systemic nocardiosis (Baikie *et al.*, 1970; Lerner and Baum, 1973; Maderazo and Quintiliani, 1974; Ripon, 1974). With the nocardia recovered in the present case, however, susceptibility testing against other antimicrobials was done by agar dilution, and the results were as reported above.

There are many reports of antibiotic susceptibility

Table 1—*continued*

(B) *OTHER OCULAR NOCARDIOSES*

Case report	*Age*	*Sex*	*Predisposing cause*	*Site of infection*	*Treatment*	*Outcome*	*Diagnostic criteria*
Smith (1952)			Cutler's implant	Chronic orbital discharge			Nocardia isolated
Smith (1952)			Corn grain trauma	Dacryocystitis			
Henderson *et al.* (1960)	49	F	Cow's tail injury	Nodular scleritis	Excision lump atropine (*a*) Chloramphenicol (*b*) Staphylococcus toxoid (*c*) Typhoid vaccine (*c*) Sulphadiazine (*b*) Sulphacetamide (*a*)	Normal eye	Positive histology
Penikett and Rees (1962)	80	F		Dacryocystitis	Curetted; chlortetracycline (*d*)	Clear	Positive culture
Davidson and Foerster (1967)	46	M	? Pulmonary, primary	Endophthalmitis	Corticosteroids (*a*, *b*)	Enucleated	Positive histology
Meyer *et al.* (1970)	76	F	Cataract extraction	Endophthalmitis	Corticosteroids (*a*, *b*) Amphotericin (*e*) Tetracycline (*b*)	Enucleated	Positive histology
Meyer *et al.* (1970)	67	M	Gunshot to chest, pneumonia	Chorioretinitis	Penicillin (*c*) Sulphadiazine (*b*) Cycloserine (*b*)	Died	Positive histology
Meyer *et al.* (1970)	56	M		Chorioretinitis OD Endophthalmitis OS	Iodides (*a*) Eviscerated	20/300	Positive histology
Burpee and Starke (1971)	20	M	Bomb injury; soft-tissue sepsis	Endophthalmitis OD	Penicillin (*c*) Limb surgery tetracycline (*b*) Chloramphenicol cephalothin (*c*) Gentamicin sulphadiazine (*b*) Kanamycin (*c*)	Enucleation 20/20 OS	Positive blood and eye culture
Panijayanond *et al.* (1972)	30	M	Renal transplantation Immunosuppression Nephric abscess	Endophthalmitis	Cycloserine (*b*) Sulphisoxazole (*b*)	Enucleation	Positive culture Submandibular gland, nephric abscess
Jampol *et al.* (1973)	40	M	Arm abscess	Episcleritis	Streptomycin (*c*)	Died	Positive culture, arm
			Renal transplant Pulmonary abscess	Chorioretinitis	Sulphisoxazole (*b*) Sulphadiazine (*b*) Ampicillin		Positive culture, eye
Sher *et al.* (1977)	38	M	Hypogammaglobulinaemia	Endophthalmitis OS	Vitrectomy	20/200	Blood and pulmonary
			Pulmonary nocardiosis	Chorioretinitis OD	Ampicillin (*e*) Atropine (*a*) Dexamethasone (*a*) Neomycin (*a*) Minocycline (*b*) Erythromycin (*c*)		Positive, vitreous histology
Rogers and Johnson (1977)	77	F	Malignant lymphoma	Endophthalmitis		Died	Positive necropsy
			Immunosuppression	Necropsy diagnosis			Histology

of nocardia (Black and McNellis, 1971; Bach *et al.*, 1973; Lerner and Baum, 1973). It is difficult to compare the results of our single strain of nocardia with those in the literature, since different strains vary in susceptibility. There are numerous problems and variations inherent in the testing (Lerner and Baum, 1973; Bach, 1975). However, our method of susceptibility testing, which closely follows the method of Wallace *et al.* (1977), produced results similar to theirs.

Because nocardia tends to grow in clumps it is difficult to prepare uniform and reproducible suspensions containing equivalent numbers of organisms. In addition, in-vitro susceptibility is influenced by pH and type of agar used in the assay. Variation in these parameters may well explain conflicts in results of susceptibility testing reported in the past. Further, in-vitro susceptibility may not correlate well with clinical response (Black and McNellis, 1971; Bach *et al.*, 1973; Lerner and Baum, 1973; Lennette *et al.*, 1974). For example, cycloserine or even the sulphonamides may appear ineffective by in-vitro testing despite a good clinical response.

After the present case 2 further isolates of *Nocardia asteroides* were obtained from 2 other patients with non-ocular nocardiosis. Antimicrobial susceptibility testing was performed as before. Marked differences from the present results were obtained with some of the antibiotics. We can conclude that susceptibility testing will continue to be difficult to evaluate until standardised methods of testing for this species are established.

The favourable long-term result in this case appears to have been achieved by covering the cornea with a conjunctival flap, followed by penetrating keratoplasty 24 months later.

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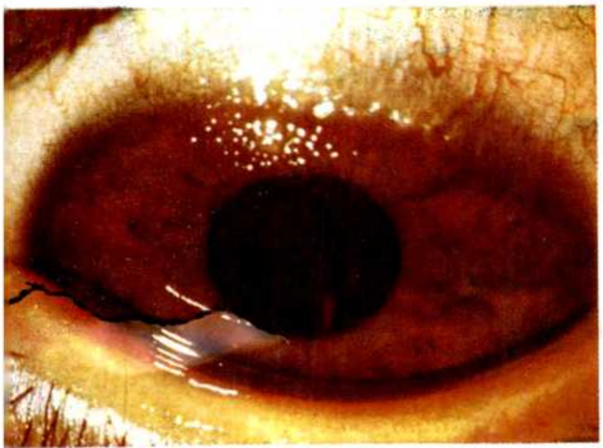
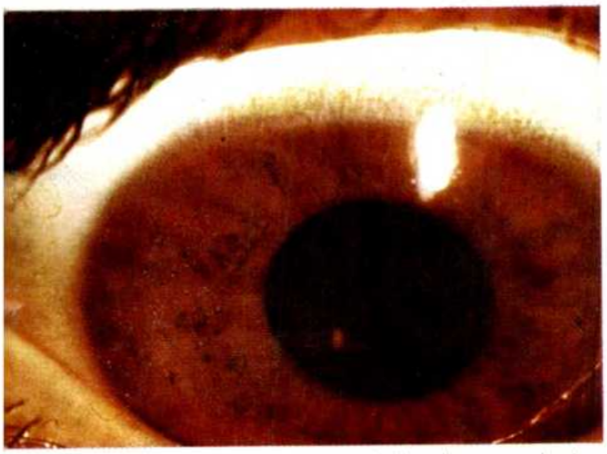


a. The superior limbus in a placebo treated eye of a patient suffering from vernal kerato-conjunctivitis, stained with fluorescein. Note the limbal hyperaemia and swelling and the irregularity of the corneal surface.



b. The opposite eye of the same patient treated with sodium cromoglycate eye drops. Before treatment, both eyes appeared similar.

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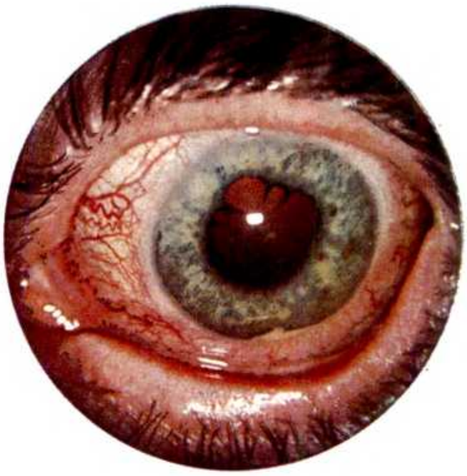

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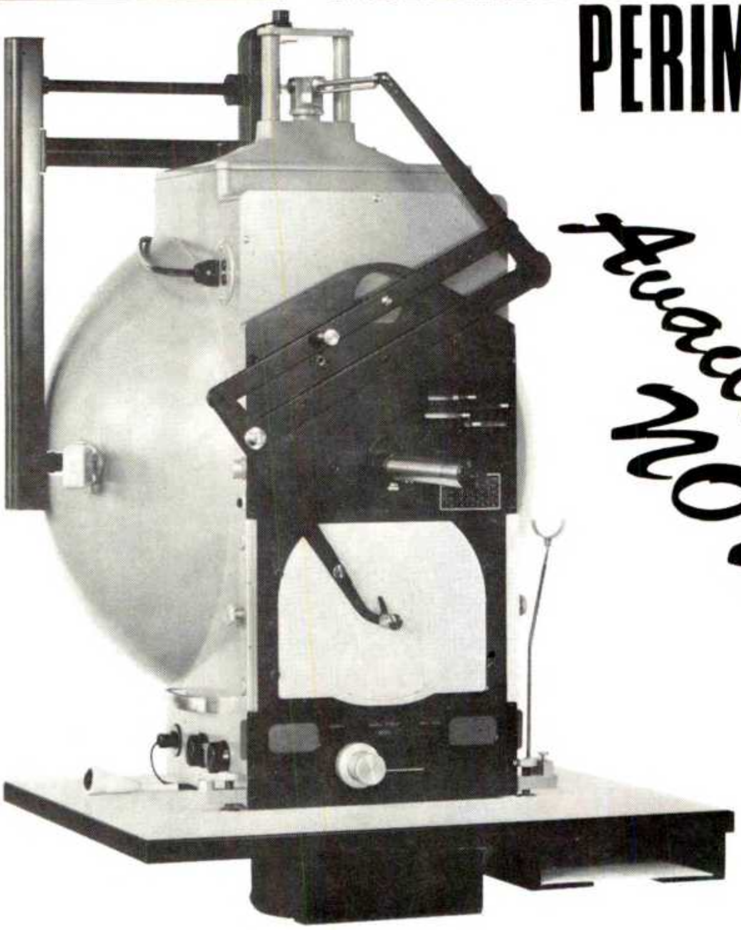

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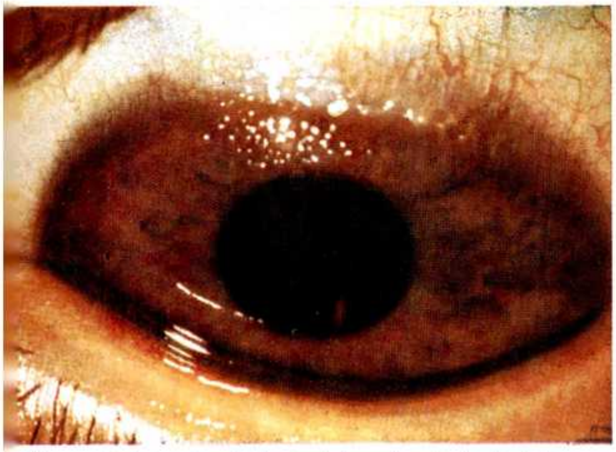

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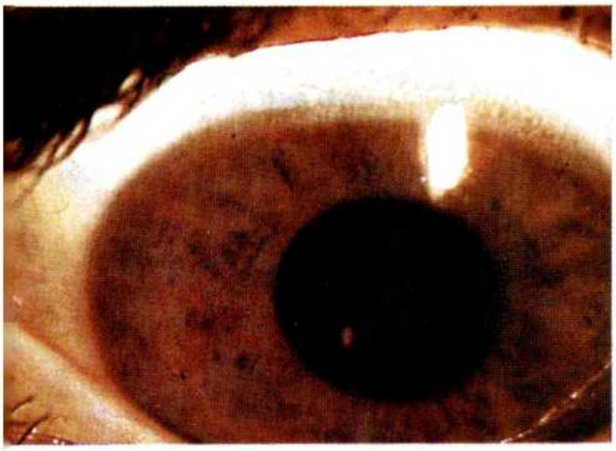

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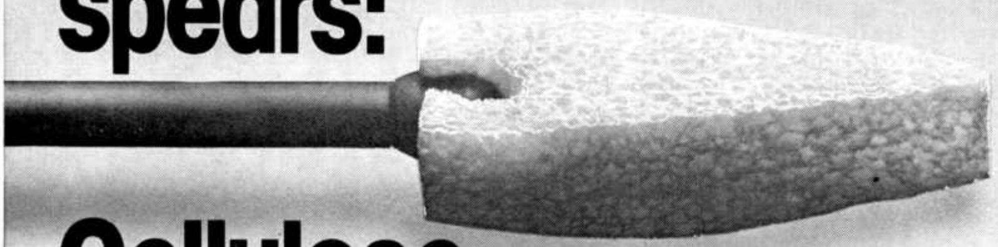

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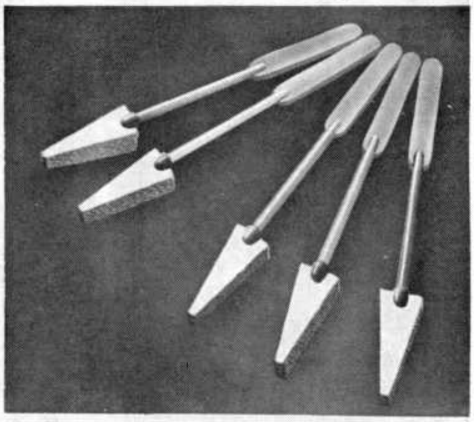

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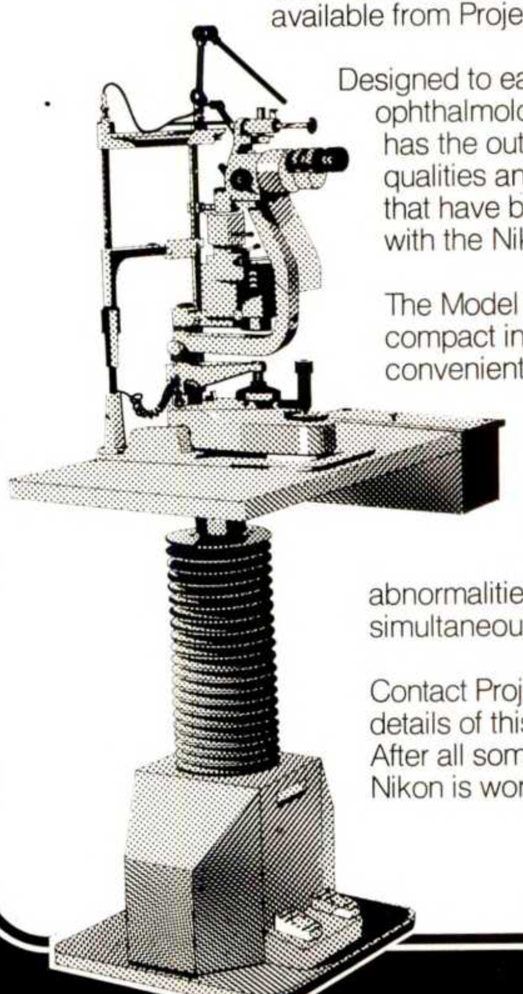

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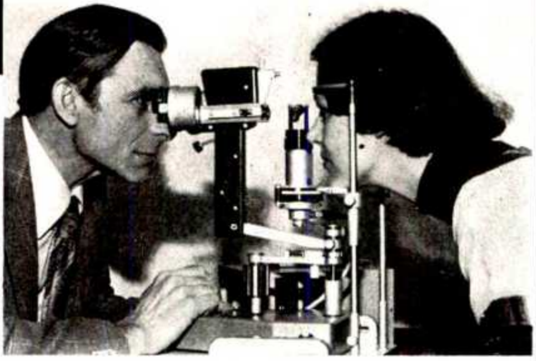

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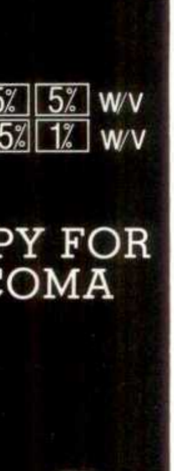

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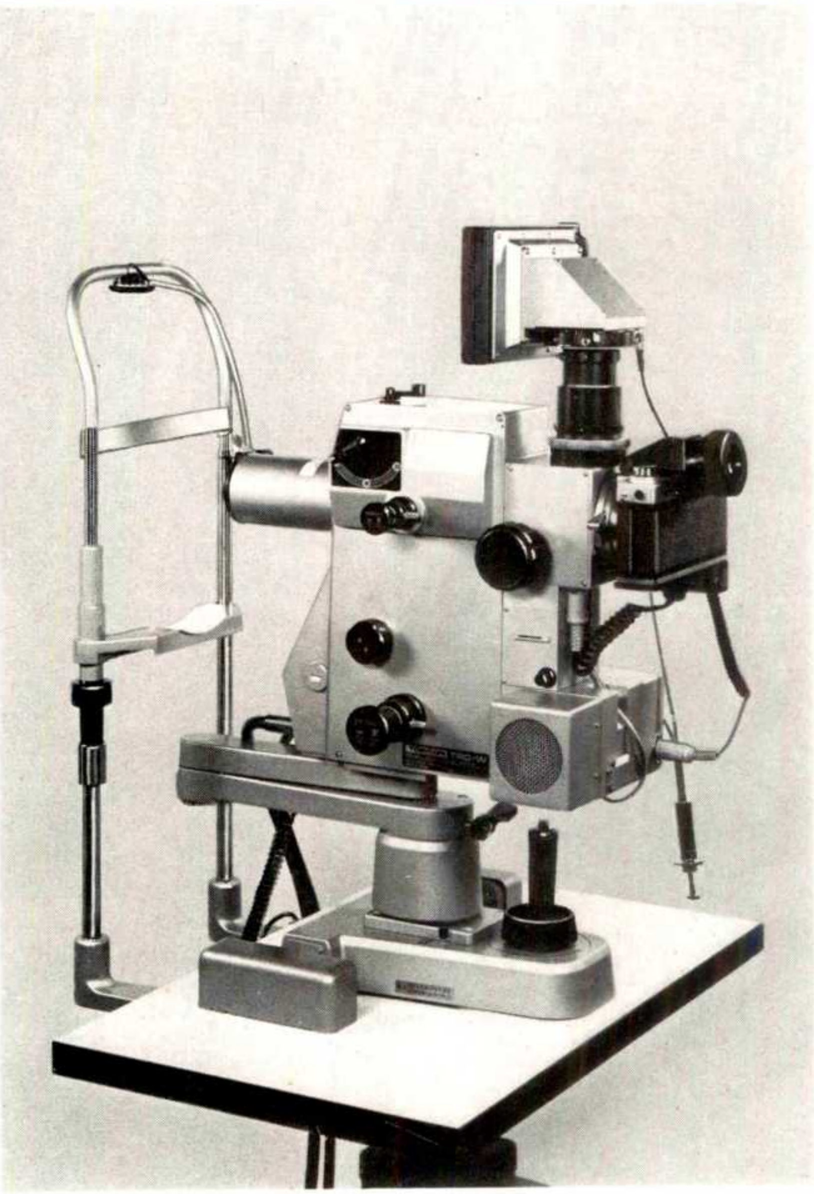

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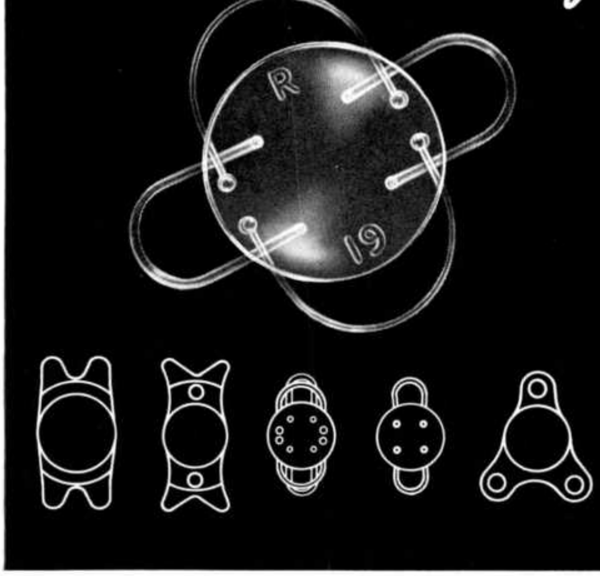

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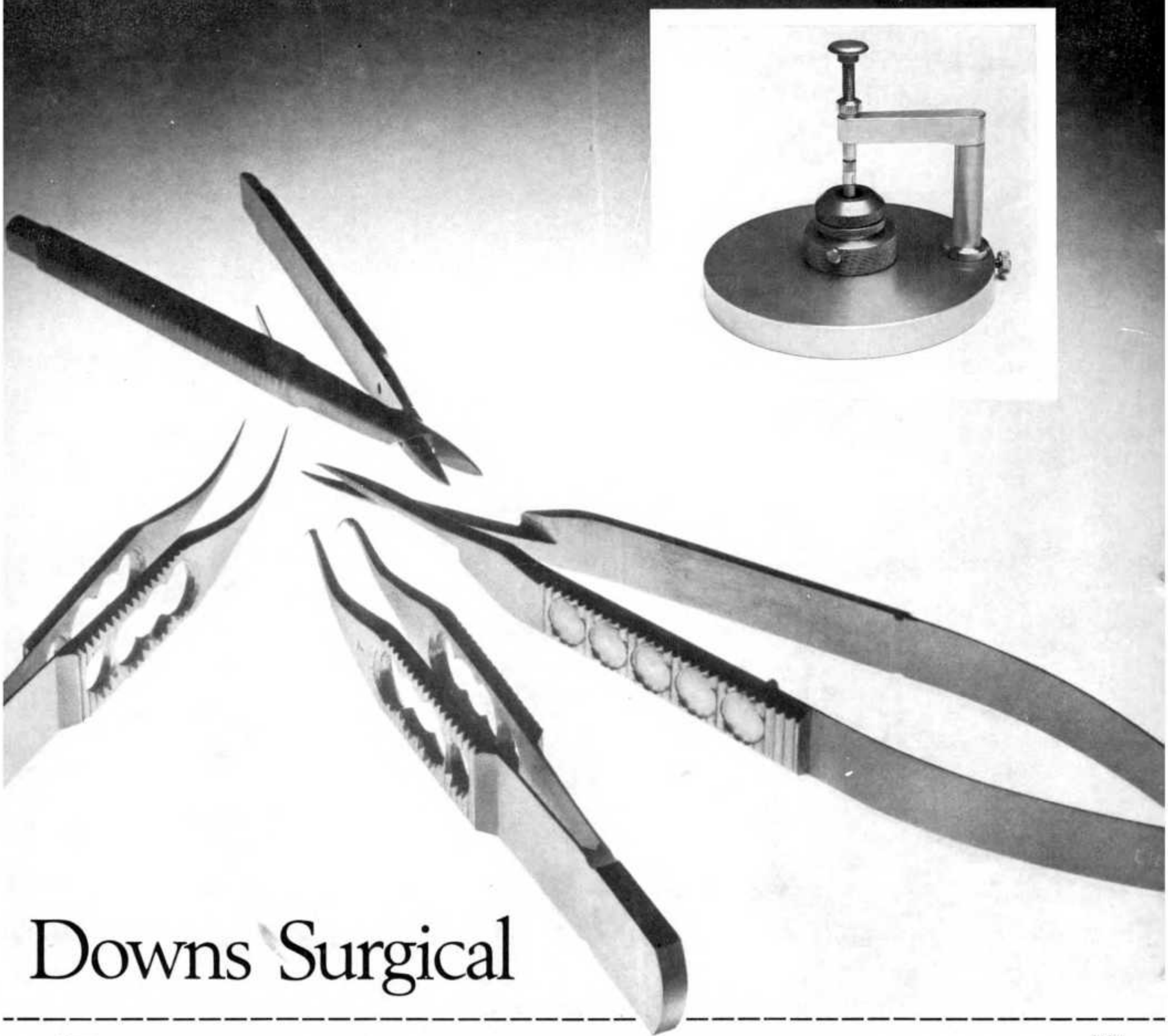

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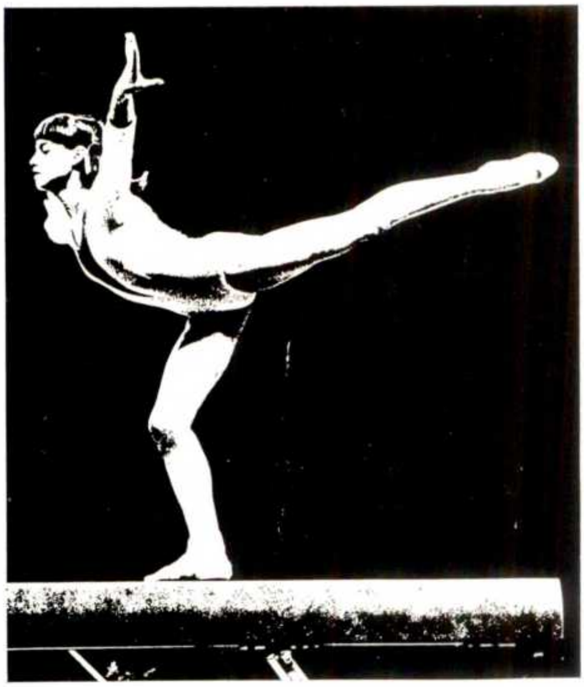

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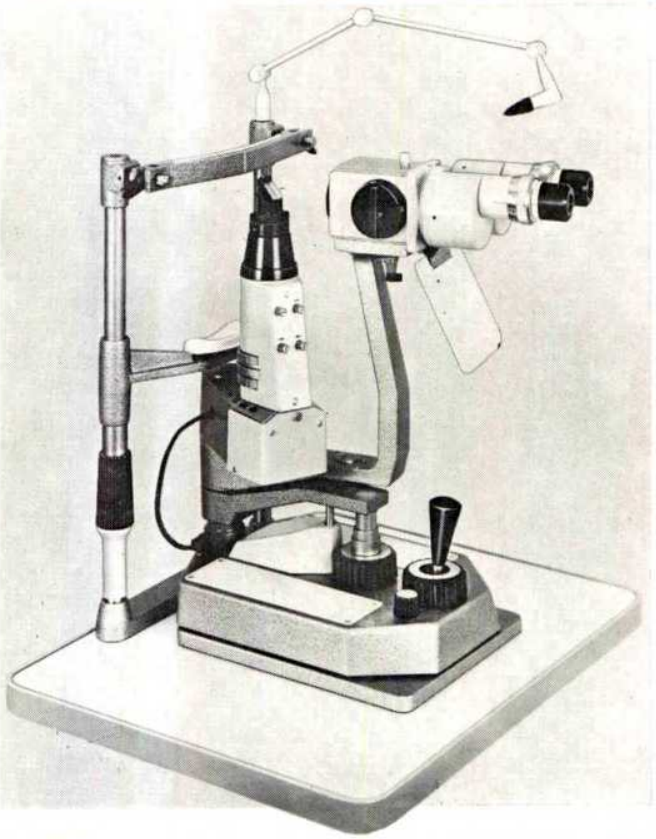

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British Journal of Ophthalmology, 1979, **63**, 455–456

Editorial: Ocular effects of ionising radiation: past and present problems

At the turn of the century the harmful effects of ionising radiation had been recognised (Birch-Hirschfeld, 1904). Information had been obtained from the use of *x* rays in the diagnosis and treatment of human disease, and this was soon supplemented by a study of the adult rabbit after exposure to ionising radiation of ill defined strength. Initially it was thought that the chief ocular effects of such radiation were confined to the skin of the lids, the cornea, and conjunctiva.

Since then a better understanding of the biological effects of radiation has been achieved by greatly improved methods of measuring the dosage and a realisation that, apart from the type, the age of the tissue is also very important. As a result a number of theories have been evolved to account for these effects and also to explain the usually considerable time lag between exposure and biological change. Briefly these theories are of 2 types and postulate either a direct or an indirect action on cells. The first group of theories, 'the direct hit theory', presumes that radiation has a direct action on the large protein macromolecules of the cell and alters them in some way. But the relative importance of the nucleus and the cytoplasm in these processes is debated. The second group of theories presumes that the change is initially in the cellular water, the radiation providing free radicles and their subsequent reaction with cellular enzymes producing harmful effects. Some credence to this idea is given by the fact that compounds such as cysteine which react readily with free radicles can protect animals to a limited extent from the ill effects of radiation. The delay is more difficult to explain, and any explanation is usually linked with the high sensitivity of rapidly growing tissue, selective harmful effects being only fully revealed when cells attempt to replicate. Thus if growth is slow the harm is long delayed.

This delayed action of ionising radiation is well illustrated by its effect on the conjunctiva and cornea. In the conjunctiva there is an initial acute reaction, with hyperaemia, oedema, and often a mucopurulent discharge. This settles down after a few weeks, but after months or years intense scarring is produced, often with symblepharon, while the blood vessels show telangiectasia. The cornea initially responds with a punctate keratopathy, which usually persists for months and is unresponsive to treatment. Eventually large ulcerated areas may suddenly appear, with a gross loss of corneal substance. After this repair is usually imperfect and slow.

The action of ionising radiation on the lens was thought to be negligible because experiments conducted on the adult rabbit at first failed to produce a cataract. It is now known that the lens of the mature animal is much more resistant to radiation. The production of cataract by this means was confined to animals in utero. However, since the epithelium of the lens, like epithelium elsewhere, continues to divide throughout life, it would be expected that the lens would also show changes which indicate that it is sensitive to ionising radiation.

Again, the effect was missed at first because it is delayed by months or years when exposure is with rays of moderate intensity—the only type available to early investigators. Since the part of the lens affected by cataractous change is the posterior pole, it could be argued that the effect is an indirect one and perhaps relates to the nutrition of the eye as a whole.

In contradiction to this, it has recently been shown (Fisher and Wakely, 1976) that the probable cause of this posterior cortical response to injury in general is the unusual growth properties of lens cells originating from the front of the lens. At the end of the second world war owing to the exposure of victims to intense gamma rays from atomic bombing a series of reports (Cogan *et al.*, 1952) appeared on the acute effects of intense radiation of the lens. These reports indicated that the long known posterior cortical changes were intensified and occurred within 6 months to 2 years. The periphery of the cataractous area was particularly dense, and a so-called doughnut-looking opacity was produced. At this stage the cataract might remain quiescent or become opaque and mature within a few months.

In clinical practice cataract has been produced when it has been difficult to shield the eye from cobalt beam or *x*-ray therapy, these procedures being necessary in the treatment of carcinoma of tissues in or around the orbit (Lederman, 1964). These cataractous lenses, when they have been examined histologically, have usually been mature. Such changes as have been reported indicate

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metaplasia of the lens epithelial cells, with the production of swollen bladder-like cells or cells which resemble fibroblasts.

From considerations of public health, however, the effect of low-dosage, possibly intermittent radiation is more important. This aspect of the problem appears to have been neglected because of the difficulty of having reliable evidence that the cataract, when present, has been caused by such exposure.

A paper in the present issue (page 457) attempts to provide a small amount of this necessary information. Again, exposure to low dosage radiation results in a very long latent period—some 25 to 30 years before a cataract of sufficient magnitude develops to impair vision seriously. It has been possible to examine such lenses by the slit-lamp and electron microscope, and 2 additional responses of the lens substance are reported in this paper.

Firstly, after the initial exposure of some years' duration there was subsequent recovery and the laying down of clear and apparently normal lens fibres. Eventually, when the function of the lens epithelium began to fail, a posterior cataract opacity with unremarkable features developed. Secondly, failure of function of the lens epithelium was characterised by a vertical rather than horizontal grouping of cells in relation to the overlying capsule, while smaller disorganised cells were not found.

At present the importance of radiational injury of the lens as a hazard in certain occupations is not clearly understood. There is no doubt that intense radiation in the region of the eyeball usually produces cataract, but it does not follow—as is commonly supposed—that intermittent low-dosage exposure is ultimately as dangerous. Similar remarks could equally apply to the present state of our knowledge in regard to ultrasonic radiations.

To overcome these difficulties it is necessary to link 2 groups of workers matched for age, one group who are exposed to such intermittent risks, and the other group who have a similar environment in other aspects but who are not so exposed. In the case of ionising radiation, workers in nuclear power installations are probably the only choice. In microwave radiation such a study could be undertaken among armed Forces personnel who service radar equipment and those who do not. Such a study would enable an estimate of the true risk of low-dose, intermittent, and long-duration radiation to be made. Unfortunately at present, without such a study, the hazard remains undetermined.

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British Journal of Ophthalmology, 1979, **63**, 457–464

Influence of a prolonged period of low-dosage *x*-rays on the optic and ultrastructural appearances of cataract of the human lens

B. P. HAYES AND R. F. FISHER

From the Department of Visual Science, Institute of Ophthalmology, London

SUMMARY Human lenses extracted for cataract 26 years after long-term exposure to an imperfectly shielded radium source were examined by slit-lamp photography, thin-section light microscopy, and electron microscopy. Anterior epithelial cells were fibroblast-like, and germinal epithelium and vacuolated cortical fibres had accumulated at the equator. A zone of light scatter at the anterior pole corresponded to an area of breakdown of cortical lens fibres, where unusual feathery fibres were orientated perpendicular to the lens surface. Two zones of light scatter separated by a 250-μm clear interval were seen in the posterior cortex. The zone at the posterior pole corresponded to an area of fibre liquefaction and large rounded membrane whorls, while the deeper zone comprised small flattened membrane whorls. The characteristic plaques of swollen abnormal cells described in previous histological studies of *x*-ray cataract were not present. This and other differences probably reflect the extremely long time course and repeated subliminal doses to which the patient was exposed.

Previous histological studies of both human and experimental *x*-radiation cataracts have mainly dealt with short-term changes developing after high radiation doses (for references see Duke-Elder, 1972; Hanna, 1975; Palva and Palkama, 1978). These studies indicate that *x*-rays act primarily on the germinal epithelial cells at the lens equator, and the cells divide to form defective lens fibres, which accumulate in plaques near the anterior and posterior poles. The breakdown of these defective fibres gives characteristic opacities in an anterior subcapsular zone and disc-shaped opacities in the posterior cortex (Hogan and Zimmerman, 1962).

In this study slit-lamp photography, and light and electron microscopy are used to investigate cataractous changes in human lenses which appeared many years after prolonged exposure to repeated low doses of *x*-radiation over a period of 11 years. The structure of the lenses is compared with that found in previous studies of *x*-ray cataract, in normal lenses (Hogan *et al.*, 1971), and senile cataract.

Materials and methods

The lenses were obtained after routine cataract extraction from a patient whose visual acuity had been reduced to 6/24 in each eye. Before cataract extraction the patient had been subjected to an imperfectly shielded radium source (120 mg) for a few minutes 3 times a week for a period of 11 years (1935–50). From 1950 there had been no exposure to radiation until removal of his cataract 26 years later.

Whole lenses were fixed by immersion in 4 changes of 3% glutaraldehyde in 0·1 M Sorenson's phosphate buffer pH 7·3 containing 0·1% $CaCl_2$ for 4 hours at 4°C. They were washed 10 times with the same buffer with 9% sucrose added and postfixed in 4 changes of 1% OsO_4 in White's solution (Wakely, 1974) overnight at 4°C. The lenses were bisected through the lens axis, block stained with buffered uranyl acetate (Brightman and Reese, 1969), dehydrated, and then embedded in Araldite. Light and electron microscope sections were cut approximately perpendicular to the surface of the lens in the regions of the anterior pole, equator, and posterior pole. Light microscope sections were stained with 1% toluidine blue/borax and electron microscope sections with ethanolic uranyl acetate and alkaline lead citrate (Reynolds, 1963).

Results

SLIT-LAMP APPEARANCES

Fig. 1. View of anterior cortex. There is a dense area of scatter just below the capsule in the region of the anterior pole of the lens, and also isolated areas

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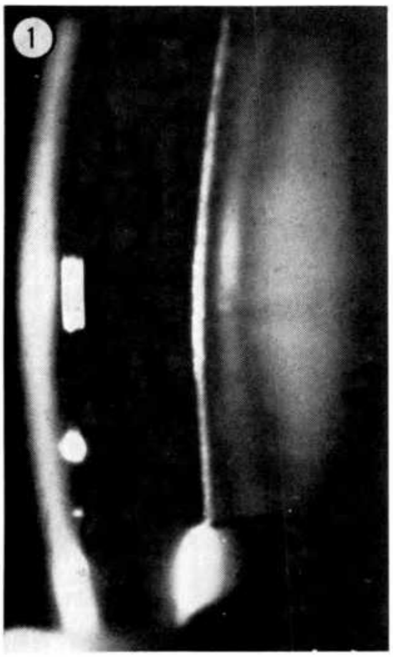


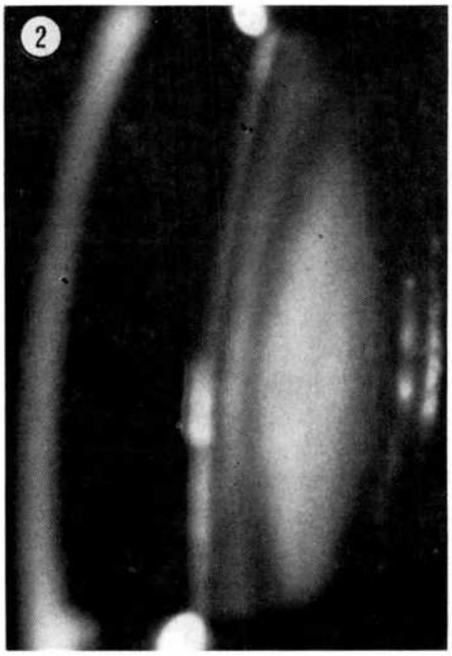


Fig. 1 *Slit-lamp view of anterior portion of the lens showing subcapsular opacification*

Fig. 2 *Slit-lamp view of posterior portion of the lens showing two areas of scatter separated by a clear interval*

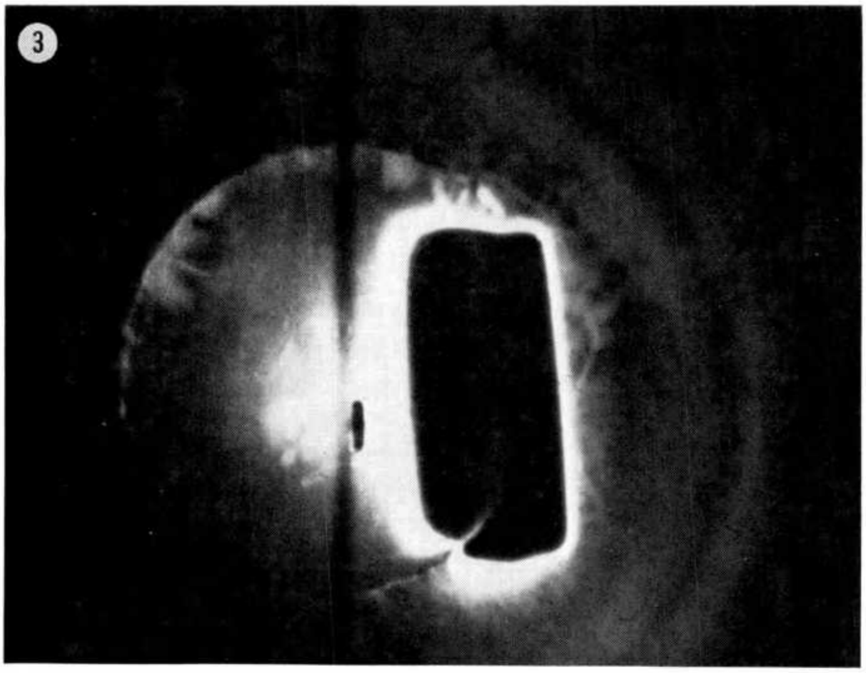


Fig. 3 *Slit-lamp view of posterior portion of the lens by reflected light showing some isolated areas of scatter at the periphery of the opacity*

which are again subcapsular out as far as the edge of the iris. The electron microscopy of these areas is shown in Figs. 4–10 and corresponds to feather fibres and the large vacuolated cells.

Fig. 2. View of posterior cortex. Two yellowish areas of scatter are seen in the posterior cortex separated by a clear interval. At the posterior pole of the lens the scatter area corresponds to Fig. 11. The other area between the posterior pole and nucleus corresponds to Fig. 14. Neither area has a

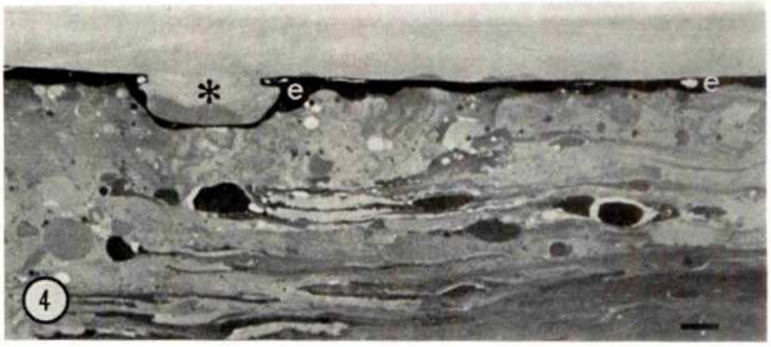


Fig. 4 *1 μm light microscope section of the anterior capsule, epithelium, and lens cortex. The asterisk marks a local thickening of the lens capsule from 15 to 28 μm. The spindle-shaped epithelial cells (e) are very darkly stained. Lens fibres show swelling, shrinkage, and dark granules. ×490; scale line 10 μm*

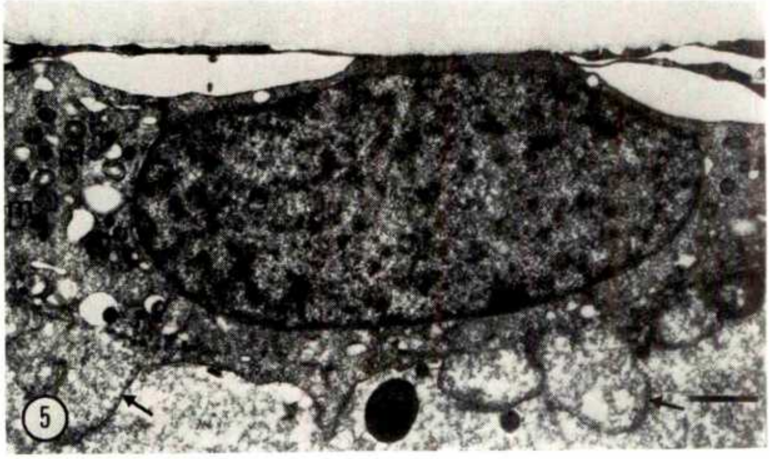


Fig. 5 *Spindle-shaped anterior epithelial cell with rounded processes (arrows) extending into the cortex. The cell contains many densely stained mitochondria (m). ×8900; scale line 1 μm*

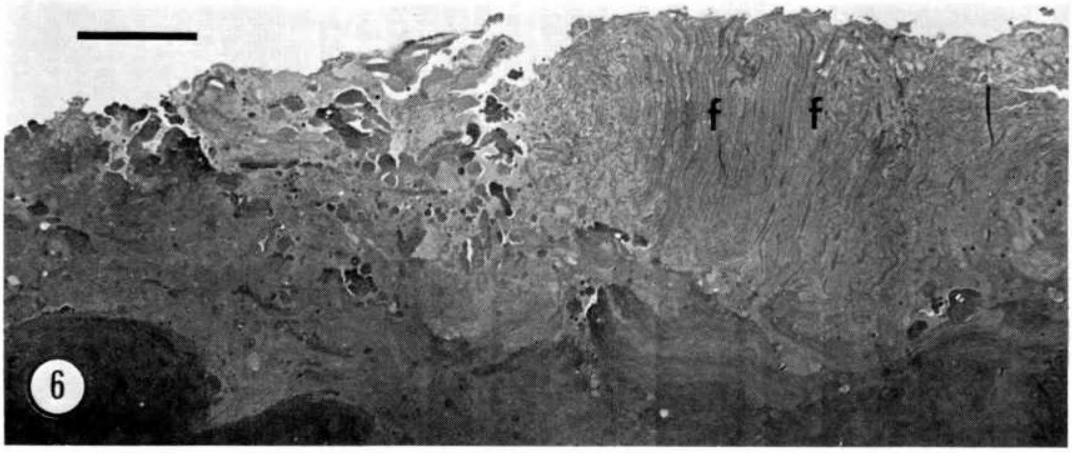
typical bivalve appearance which is seen in severe radiation cataract, for example, atomic bomb radiation. In addition at the periphery there are some irregular areas of scatter which do not correspond to cuneiform-like opacities which would be seen on retro-illumination. These areas produce scatter by reason of the irregularity of the lens fibres, which are overlaid by vacuolated areas (Fig. 10).

Fig. 3. View by retro-illumination. A circular area of increased scatter is shown at the posterior pole of the lens together with some irregular areas at the lens periphery. These appearances do not show the markedly increased scatter at its edge producing a ring-shaped bounded area characteristic of acute radiation cataract. However, the margins of the area are more clearly defined when compared with senile cupuliform cataract. (From the measurement of slit-lamp photographs the clear interval between these areas is about 250 μm thick. This corresponds to a period of about 30 to 35 years for the fibres to be laid down [Fisher, 1970].)

LIGHT AND ELECTRON MICROSCOPY

Anterior lens. The thin epithelium at the anterior pole (1 to 3 μm thick) comprised darkly stained spindle-shaped cells up to 30 μm long (Fig. 4). Occasional breaks were found in the epithelium, and many cells contained large vacuoles. The capsule at the anterior pole was usually about 17 μm thick, but a small area was found where capsule thickness increased to 29 μm (Fig. 4); the spindle-shaped epithelial cells were here depressed into the lens cortex. Away from the anterior pole the epithelium was thicker (5 μm) and the cells were less densely stained. These epithelial cells were unusual in having many dark mitochondria and a number of rounded projections into the lens cortex (Fig. 5).

An area of liquefaction of the superficial cortical lens fibres, 200 μm deep, was observed at the anterior pole, containing feathery filaments orientated mainly perpendicular to the lens surface (Fig. 6). Electron microscopy showed that the matrix of this watery area and of the filaments resembled the fine granular cytoplasmic matrix of intact lens fibres (Fig. 7). The feathery filaments, a maximum of 20 μm wide and 200 μm long, were only partly contained by cell membrane, junctional membranes being particularly well preserved. Among the filaments dense granules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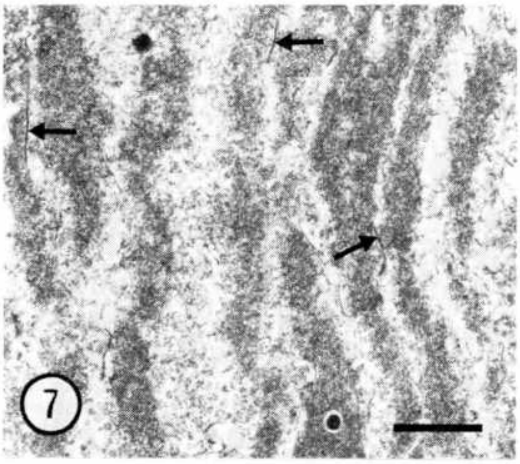
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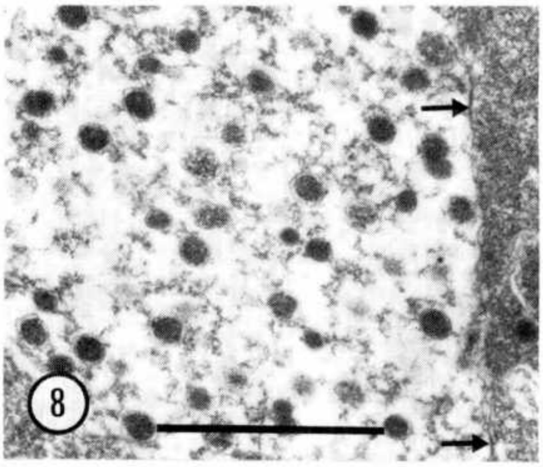
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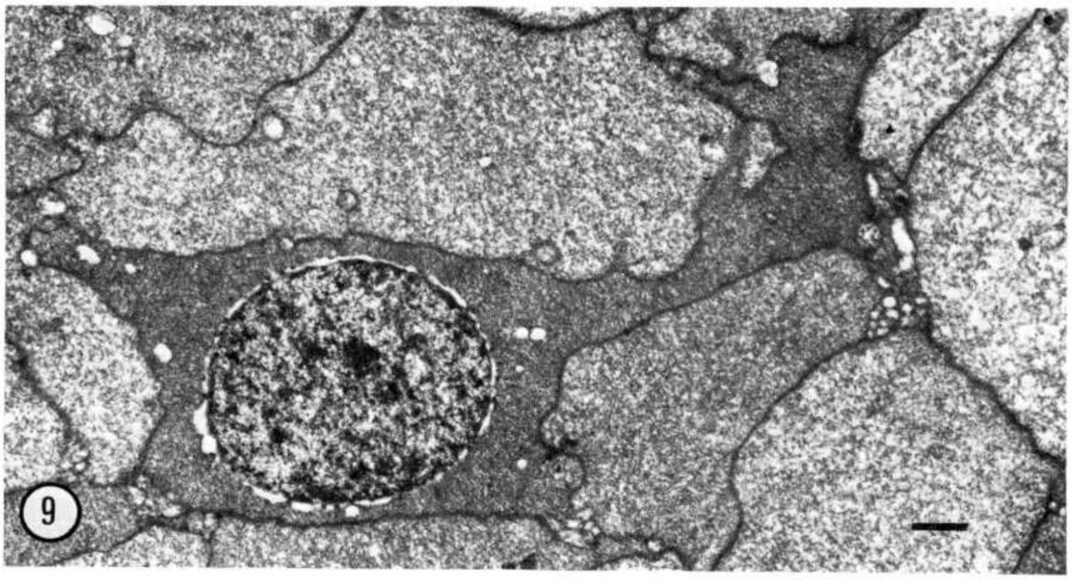
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(0·1 to 0·3 μm diameter) were found. At the edge of the filamentous area cortical lens fibres were swollen and dense membrane-bound granules, up to 1 μm diameter, were common (Fig. 8). Swollen lens fibres reached 10 μm diameter and were bounded by fragmentary cell membranes, occasionally fused to small membrane whorls (Fig. 6). Other superficial cortical fibres (to a depth of about 50 μm) had a more normal ultrastructural appearance although they varied in diameter (up to 8 μm) and were undulating in outline (Fig. 9). Nucleated fibres with amoeboid outlines were occasionally seen among them (Fig. 9). Deeper cortical fibres were dense and shrunken with wavy outlines (Figs. 4 and 6).

Equator. Towards the equator the epithelial cells gradually became less spindle shaped and more cuboidal in shape, the epithelium was about 10 μm thick (normal thickness 15 μm), and the cells contained many vacuoles next to the capsule (Fig. 10). Between the epithelium and lens fibres was a darkly stained layer about 0·5 μm deep. At the equator the germinal epithelium formed a plaque of cells with oval palely stained cell bodies about 3 cells (22 μm) thick. Extending anteriorly beneath the epithelium and posteriorly beneath the capsule for about 200 μm was a layer of unusually fine fibres with diameters of 1 μm or less and containing many small vacuoles. Beneath these fibres the superficial cortex appeared to be normal to a depth of 90 μm where fibre swelling was marked. Deeper in the cortex fibres were darkly stained, undulating, and fragmented as in the deep anterior cortex.

Posterior lens. The lens capsule at the posterior pole, which had artefactually lifted away from the cortex, was of normal thickness (approx. 3 μm). The posterior pole showed liquefaction of cortical lens fibres to a depth of 150 μm in the right and 500 μm in the left lens. The watery area contained little granular or filamentous debris when compared with the anterior pole (compare Figs. 6 and 11). Debris in the watery area was in the form of dense membrane-bound granules up to 5 μm diameter and membrane fragments and whorls (Fig. 12). At the margin of the area of liquefaction the shrunken wavy cortical fibres had swollen rounded tips (Fig. 11), and similar rounded profiles with a matrix like that of cortical lens fibres were found in the watery area (Figs. 11 and 12). Subcapsular fibres at the posterior surface to the side of the watery area were disorganised to a depth of 40 μm, some being swollen while others were dense and appeared shrunken (Fig. 13). Large rounded membrane whorls, maximum diameter 2 μm, were found between the fibres, made up of stacks of fused membranes with a complex folded pattern (Fig. 13). In the right lens a further zone of membrane whorls was observed parallel to the posterior lens surface and localised beneath the watery area at 200 to 260 μm depth. Here the membrane whorls were flattened parallel to the lens fibres and the fused membranes continuous with the lens fibre cell membranes (Fig. 14).

Discussion

When the fine structure of the cataractous lenses is compared to that of the normal human lens (Hogan *et al.*, 1971; Kobayashi and Suzuki, 1975), the greatest changes are seen in the lens epithelium, anterior and posterior cortex. The lens capsule has a normal appearance and thickness except for a local thickening near the anterior pole, where the epithelium is depressed into the cortex. Local depressions of this type are thought to be the sites of elimination of lens fibre debris into the capsule and are common in senile cataract (Brini *et al.*, 1963). In a histological study of ionising radiation cataracts by Cogan *et al.* (1952) thickening of the posterior capsule was, however, consistently observed.

Other common features of previous histological studies of *x*-radiation cataract are subcapsular plaques of epithelial cells, particularly at the posterior pole, where these are often swollen to form bladder or Wedl cells (Cogan and Donaldson, 1951; Cogan *et al.*, 1952; Fujinaga, 1973; Hanna, 1975; Palva and Palkama, 1978). No plaques are found in this study, but rare nucleated lens fibres occur in the anterior cortex. The anterior epithelium is extremely thin

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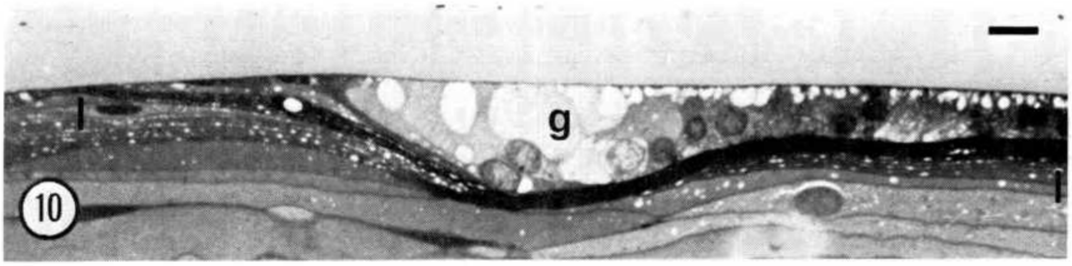
Fig. 6 *Light micrograph of lens cortex near the anterior pole. Many swollen and shrunken lens fibres and fine granules can be seen on the left of the micrograph, and on the right feathery fibres (f) are orientated perpendicular to the lens surface. The capsule was lifted away from the anterior lens during dissection. ×160; scale line 100 μm*

Fig. 7 *Electron micrograph of the feathery fibres shown in Fig. 6. Fragments of cell membrane occur between them. Junctional membrane: arrows. ×11 800; scale line 1 μm*

Fig. 8 *Intracellular granules and junctional membranes (arrows) of the swollen lens fibres in the anterior cortex. The dense granules have a similar matrix to the lens fibres and most are approximately 0·1 μm diameter. ×30 000; scale line 1 μm*

Fig. 9 *Nucleated cell in the anterior cortex has processes extending between the swollen misshapen lens fibres. ×7600; scale line 1 μm*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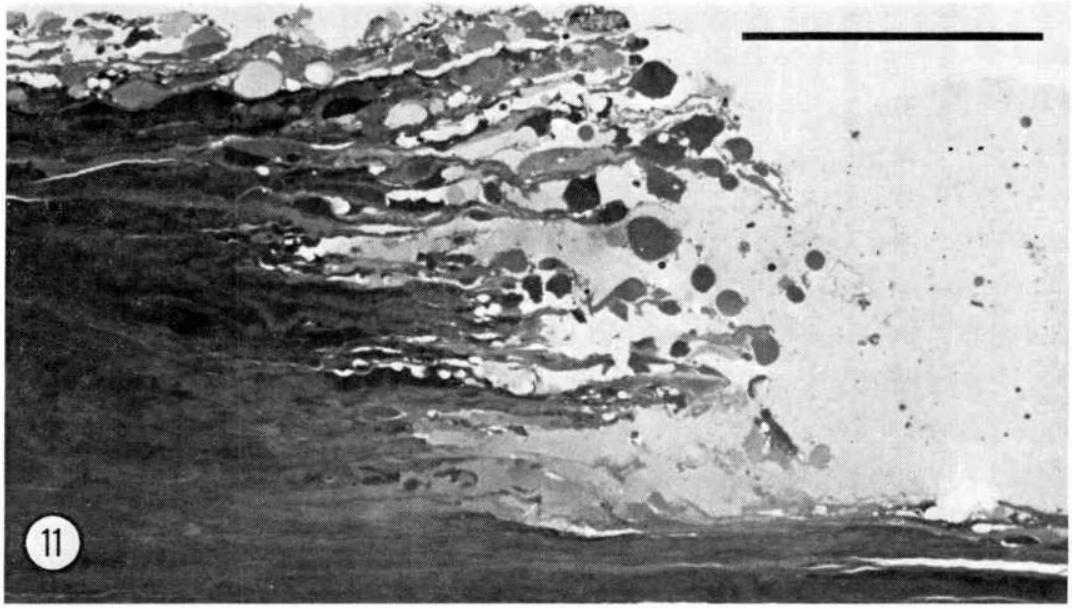
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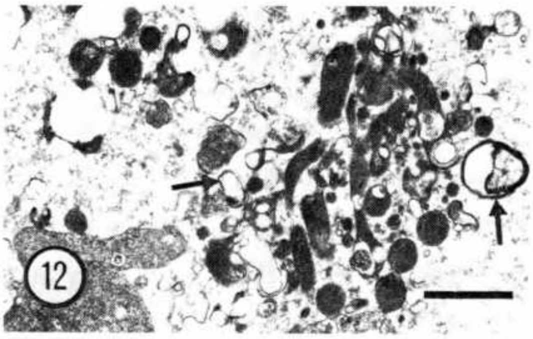
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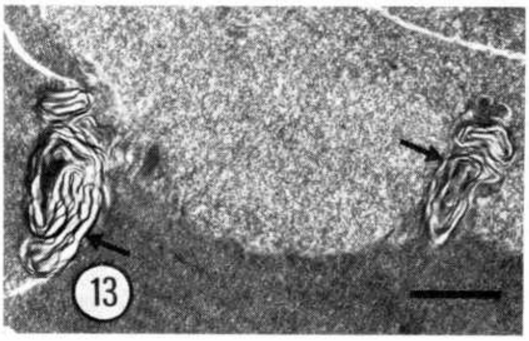
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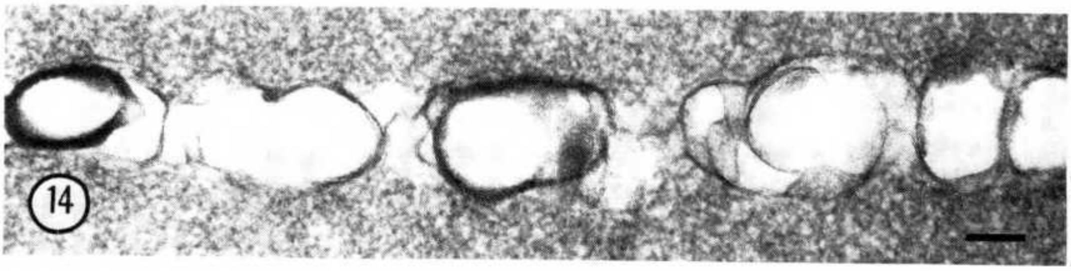
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and discontinuous; the epithelial cells are spindle shaped in section and about 30 μm diameter instead of their normal 20 μm (Hogan *et al.*, 1971). There is reduced interdigitation between the cells; they contain many darkly stained mitochondria and have projections into the cortex (see Palva and Palkama, 1978). This patchy, fibroblast-like anterior epithelium has previously been found after irradiation (Cogan *et al.*, 1952; Hanna, 1975).

Low doses of radiation are thought to act on the germinal epithelial cells at the lens equator causing accelerated defective cell division (Hanna, 1975). Lens fibres formed from these cells fail to elongate, lose their cellular attachments, and become vacuolated. In this study an accumulation of epithelial cells and shrunken vacuolated cortical fibres occurs at the equator suggesting that the germinal epithelium has been damaged and is unable to form normal lens fibres. Other superficial equatorial cortical fibres are slightly swollen but otherwise normal (Hogan *et al.*, 1971). Deeper cortical fibres are darkly stained, shrunken, and fragmented like normal nuclear fibres or the cortical fibres of senile cataracts (Kobayashi and Suzuki, 1975).

Zones of cortical liquefaction are found at the anterior and posterior poles consistent with the clinical appearance of late stage *x*-ray cataract, that is, disc-shaped polar cortical opacities (Duke-Elder, 1972). At the edges of the liquefied zones a variety of degenerative changes are seen in the cortical lens fibres—shrinkage of fibres and breakdown of their cell membranes, swelling of fibre tips, and the formation of small dense intracellular membrane-bound granules. The watery areas contain the products of this degeneration. For instance, the large round globules are probably the pinched-off swollen tips of cortical fibres and may correspond to the morgagnian globules found in more mature cortical cataracts (Hogan and Zimmerman, 1962). Membrane fragments and small dense granules are also found here.

The most striking feature of the anterior area of liquefaction is the feathery fibres orientated perpendicular to the lens surface, bounded by incomplete cell membranes. These shrunken realigned cortical fibres do not appear to have been described in previous histological studies of cataract. In the posterior cortex bordering the watery area damage to the cortical fibre cell membranes is apparent both as fragmentation and as large rounded membrane whorls of fused cell membranes. Somewhat larger whorls are found in mature posterior cortical cataract (Hayes, unpublished). The yellowish area of light scatter seen in the slit lamp at the posterior pole probably includes both the watery area and the surrounding region of cortical fibre membrane damage.

A deeper zone of light scatter between the pole and the nucleus corresponds closely in depth and lateral spread with the distribution of flattened membrane whorls. This may be the original zone of radiation damage to the posterior lens, subsequently buried in the lens cortex by the growth of more normal lens fibres in the 26 years after exposure to radiation (see Fisher, 1970). Fisher and Wakely (1976) showed experimentally that zones of light scatter in the lens can be produced by membrane whorls which develop several years after damage to the capsule, and Philipson (1973) has also suggested that membrane whorls cause a loss of transparency in supranuclear cuneiform cataract.

Fig. 10 *Lens equator. Epithelial cells and superficial cortical lens fibres are vacuolated. Germinal epithelial cells (g) have accumulated at the equator and a layer of thin vacuolated lens fibres (l) can be seen in the superficial cortex.* ×*650; scale line 100* μ*m*

Fig. 11 *Posterior cortex. Shrunken wavy lens fibres on the left of the micrograph have swollen tips extending into the area of liquefied lens cortex on the right. Round granules are suspended in the liquefied area which is near the posterior pole.* ×*400; scale line 100* μ*m*

Fig. 12 *Debris in the liquefied area of the posterior lens cortex consists of membrane-bound granules and membrane whorls (arrows).* ×*11 800; scale line 1* μ*m*

Fig. 13 *Posterior cortex bordering the liquefied area. Large rounded membrane whorls (arrows) are found between the distorted superficial cortical lens fibres just below the capsule.* ×*11 800; scale line 1* μ*m*

Fig. 14 *Flattened membrane whorl in the posterior cortex at a depth of about 250* μ*m below the capsule. Up to 5 membranes are fused together to form the whorl.* ×*78 000; scale line 0·1* μ*m*

We are most grateful to Mr S. Miller for the clinical material examined in this study. We would also like to thank the Moorfields Research Grant for financial support. The electron microscope used for this study was donated by the Wellcome Foundation.

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Cataract extraction complicated by capsular glaucoma

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SUMMARY Synechiae involving the iris pigment epithelium and the peripheral anterior lens capsule occur in capsular glaucoma. During cataract extraction they may bring about traction on the capsule threatening its rupture. The ultrastructural basis of these adhesions is a bonding of pigment cells to capsular surface by pseudoexfoliative material.

Tarkkhanen (1962) noted that the incidence of senile cataract in patients with unilateral pseudoexfoliation (PE) was no greater on the affected than the unaffected side. He concluded that PE disease does not appear to be pathogenically associated with cataract. In contrast, patients with capsular glaucoma have a high incidence of lens opacities. Layden and Shaffer (1974) suggested that some of these cataracts may be iatrogenic as many of these patients have been subjected to filtration procedures and long-acting anticholinesterases.

Capsular glaucoma affected about 50% of Tarkkhanen's (1962) patients with the PE syndrome. The mechanism producing capsular glaucoma is unknown. Since steroid responses are positive in more than 28% of patients (in contrast to the 90% seen in chronic simple glaucoma), Pohjola and Horsmanheimo (1971) considered it to be secondary to the PE process. Support for this contention was provided by the transmission electron microscopic (TEM) studies of Ringvold (1971), who found PE material both within and between the trabecular beams of the meshwork and, perhaps more significantly, infiltrating the juxtacanalicular connective tissue as well as within the giant vacuoles of the endothelial cells lining the proximal wall of Schlemm's canal.

It is well known that adequate mydriasis is difficult to obtain in PE disease, a circumstance which is probably due to the extensive infiltration of the iris with PE fibres, as was noted by Ghosh and Speakman (1974). These authors found PE material embedded in the anterior limiting layer, surrounding and even replacing the radial blood vessels as well as being deposited on and between the basement membrane of the iris and pigment epithelium. There is a special tendency for PE fibres in this latter site to accumulate in the circumferential furrows, where they compress the intervening epithelial ridges, producing a striped appearance macroscopically and a characteristic cogwheel outline in radial microscopic sections as noted by Yanoff and Fine (1975). PE material in this location may cause adherences of the iris to the peripheral lens capsule. Aasved (1973) found fragments of the pigment layer on the anterior lens capsule in such cases, and the 'remnants of posterior synechiae' which Krause and Tarkkhanen (1978) observed in 5 out of 100 extracted cataractous lenses affected with PE disease are presumably further evidence of this type of adhesion.

The nature, extent, and tensility of this bonding of the iris to the periphery anterior lens capsule in capsular glaucoma (and to a less extent in PE disease) has not been the subject of previous comment. The following report describes the histology of these adhesions and indicates that they are a potential cause of capsule rupture when cataract extraction is undertaken.

Material and methods

Six eyes of 6 consecutive patients with capsular glaucoma were operated on for cataract. Five of the patients had been treated with anticholinesterases for control of glaucoma. Radial iridotomies or sphincterotomies were performed to enlarge the pupil. Alpha-chymotrypsin was used in all cases. The extracted lenses were fixed in cold 2% glutaraldehyde. Selected specimens of pre-equatorial lens capsule were osmified, dehydrated, and embedded in epoxy resin before sectioning for TEM.

Results

Preoperative mydriasis in the eye scheduled for cataract extraction was limited to 5 mm or less in

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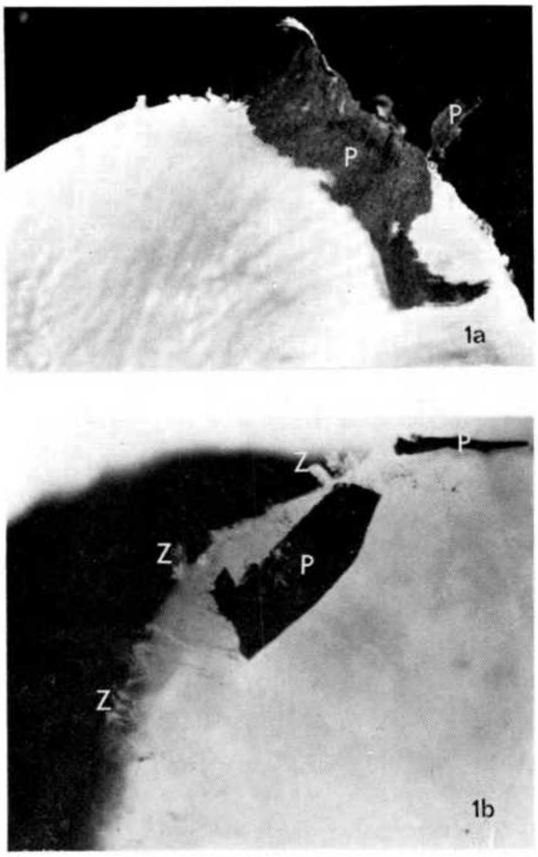

Figs. 1 (a), (b) *Sheets of iris pigment epithelium, P, are adherent to the pre-equatorial lens capsule. Zonules, Z, are encrusted with PE material. Cases 1 and 2*

every case. Neither iridodonesis nor phakodonesis was noted in any of these patients. Cataract extraction in all of the patients was protracted and the capsule thrown into traction folds until the lens was finally delivered. The extracted lenses showed 1 to 4 sheets of iris pigment epithelium which were attached to the anterior lens capsule in the pre-equatorial region (Figs. 1 and 2). In some instances the pigment sheets were rolled over, the posterior iridic surfaces showing the characteristic striping caused by PE fibres accumulated within the circular furrows (Fig. 2). Elsewhere in the pre-equatorial region and to a less extent in the granular zone there was a fine pigment stippling. Pigment granules often adhered to and defined the zonules, which more peripherally were encrusted with PE material. Some zonules were stiffened and stood out from the capsule at an acute angle for a millimetre or so.

Transpupillary transillumination of the irides postoperatively showed sharply defined defects in the pigment epithelium of the iris periphery which corresponded in size and position with the pigment sheets adherent to the extracted lenses.

An extensive bonding of the iris pigment epithelium to the pre-equatorial lens capsule by PE fibres was confirmed in TEM (Fig. 3). There was no evidence of collagenous or other fibrous union. Cell membranes of the pigment epithelial cells were often disrupted with PE fibres lying alongside various organelles. In these areas the basement membrane of the iris was also frequently absent. Occasionally bush-like excrescences of PE fibres were capped with ruptured pigment cells (Fig. 4). The lens capsule often showed surface irregularities and multilaminar basement membrane formation (Fig. 3) as well as the pathognomonic deep striated band described by Bertelson *et al.* (1964).

Discussion

Impaired mydriasis in patients with senile cataracts may be associated with the PE syndrome. Neverthe-

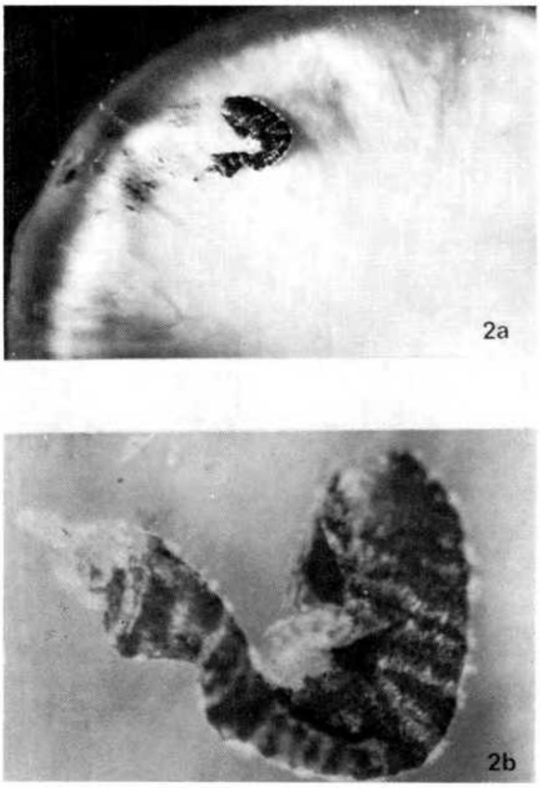

Fig. 2 (a) *Iris pigment epithelial sheet adheres to capsule, but it is rolled over to display striped appearance caused by accumulation of PE fibres in circumferential furrows. Case 3.* (b): *Detail of 2* (a)

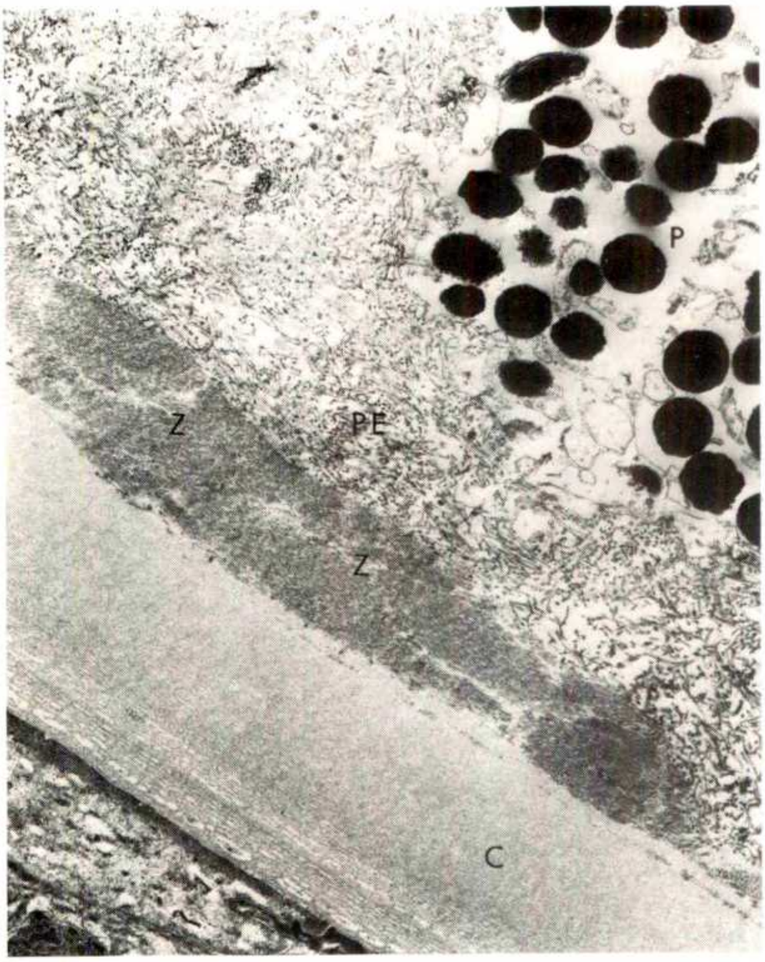

Fig. 3 *Pseudoexfoliative fibres, PE, bonding iris pigment epithelium, P, to zonules, Z, and lens capsule, C, which shows multilaminar basement membrane formation. The basement membrane of the pigment epithelial cell has almost disappeared and the cell membrane is dehiscent, so that PE fibres lie in direct contact with organelles (× 10 800)*

less, it is usually taught that cataract extraction in this disorder is relatively uncomplicated. Certainly the zonules are unduly fragile and may undergo spontaneous rupture, leading to the subluxation of the lens in some patients, as noted by Bartholomew (1970). In contrast, the present study indicates that cataract extraction, in spite of an adequately fashioned pupillary opening, may be difficult in some patients with capsular glaucoma because PE fibres often effect an extensive union of the iris pigment epithelium to the pre-equatorial lens periphery. These adhesions resist lysis with alpha-chymotrypsin. It is possible, however, that synechiotomies may be performed by sweeping an iris repositor between the lens and iris, a technique which was not used here. Peripheral bonding of the iris to the lens, together with poor dilatation of the pupil after instillation of mydriatic, has also been reported (Zaret *et al.*, 1976) in cataracts which developed after exposure to non-ionising radiant energy. Moreover, difficulty in cataract extraction was also reported in this instance. Finally, it is well recognised that pigment stippling of the anterior lens capsule as well as posterior synechiae and a poor mydriatic response may also be seen in patients who have been treated with long-acting cholinesterases for chronic simple glaucoma. The nature of these adhesions in the 2 latter conditions has not been studied.

Davanger (1977) views PE material as a fibre gel. If so, aqueous could permeate the PE material only by the slow process of diffusion, and hence mass flow would be prevented. PE material deposited between the lens and iris periphery may conceivably impede the flow of aqueous in this way, thus causing a pressure differential between the aqueous compartments resulting in forward movement of the iris with narrowing of the angles. Herbst's (1976)

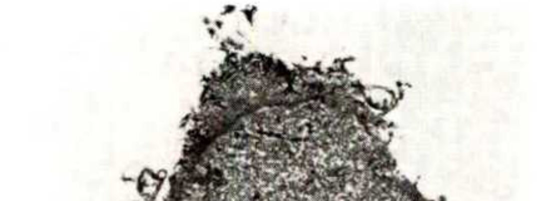

Fig. 4 *Bush-like mass of PE fibres capped by disintegrating pigment epithelial cell (× 8500)*

patient with unilateral shallow angles and ipsilateral PE disease may have been an instance of such hypothetical mechanics. Layden and Shaffer (1974) found that the incidence of narrow angles (grade 2 or less) in 100 patients with PE syndrome was 25% in contrast to 5% of the normal population. These authors point out, however, that many of their patients were on anticholinesterases, which are known to reduce anterior chamber depth. Thus the possible role of these pre-equatorial adhesions in producing angle narrowing in the PE syndrome must for the present remain speculative.

Miss Sharon Edwards was responsible for the technical aspects of microscopy in this report.

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British Journal of Ophthalmology, 1979, **63**, 469–470

Trial of a laminated material to reduce glare in cataract

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SUMMARY A recently-introduced laminated material which accepts light only over a small angle on either side of the normal was compared to standard Polaroid sunglasses. A preliminary trial failed to show any superiority of the new material in reducing glare for patients with moderate cataract.

During the development of cataract patients experience considerable disturbance of vision before the disability warrants operation. The use of tinted glasses to reduce dazzle has been recommended (Duke-Elder, 1969). Recently the introduction of a laminated material, transmitting light only within a small angle of acceptance on either side of the normal to the surface of the material, has made it possible to try an alternative method for reducing dazzle. A pilot study has been conducted to assess its possible value in clinical practice.

Patients and methods

Ten patients, all women, with senile cataract of varying morphology were invited to take part in the study; all complained of reduced vision. The refraction of each patient's eyes was tested, and each was given spectacles with optimum correction and 2 pairs of clip-on lenses, one a standard Polaroid sunglass, the other containing the laminated material. The patents were asked to compare the value of spectacles alone and each of the two clip-on glasses in various types of lighting, outdoors and indoors, for distance and for reading. After a fortnight their reactions were assessed independently by the surgeon, who did not know which clip-on glass contained which material.

Results

Table 1 shows the ages, corrected visual acuities, and cataract morphology of the patients. Only 3 of the 10 patients, numbers 1, 8, 10, found any appreciable advantage from the clip-on glass, and in all cases the material preferred was the Polaroid. A further 4 patients, though preferring a plain spectacle correction, were able to differentiate one clip-on glass as more advantageous; 3 were in favour of Polaroid and 1 of the laminated material. Corrected visual acuity with the clip-on glass was often lower than with a plain correction.

Table 1 *Details of patients studied*

	Age	*Corrected VA right and left*	*Binocular Polaroid*	*VA with Laminated*	*Type of cataract*	*Preferred† material*
1	63	6/18:6/18	6/24	6/18	N	Polaroid
2	69	6/9:6/18	6/9	6/9	W	—
3	72	6/12:6/12	6/12	6/12	C	(Polaroid)
4	88	6/18:6/12	6/18	6/18	W	(Laminated)
5	70	6/18:6/18	6/12	6/18	W	(Polaroid)
6	71	6/12:6/18	6/18	6/24	N, W, C	(Polaroid)
7	79	6/36:6/24	6/24	6/36	W (N)	—
8	68	6/18:6/12	6/36	6/36	W	Polaroid
9	70*	6/18:6/18	6/18	6/18	W	—
10	74	6/12:6/24	6/36	6/36	N	Polaroid

VA = visual acuity. N = nuclear. W = cuneiform. C = cupuliform. *Limited trial indoors. †Entries in brackets where patients preferred plain correction.

Discussion

The majority of patients in this pilot study had cuneiform cataract, which, it was anticipated, would be most likely to produce dazzle when subjected to strong light. Only 1 of the 3 reporting favourably on the Polaroid clip-on glass had cuneiform cataract. The

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other 2 had nuclear cataract and may have benefited from the slightly enlarged pupil resulting from reduced illumination.

Admittedly this study was carried out during the autumn, when high levels of outdoor illumination are not usual, but it seems that the dazzle factor is less important than anticipated; and the use of a laminated material with directionally sensitive transmission was not particularly helpful in promoting the vision of patients with moderate cataract.

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'Silicone rubber' lenses in aphakia

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SUMMARY Tesicon, one of the commercially available 'silicone rubber' lenses, was used in the correction of aphakic patients. In 74% of cases the lenses were considered successful for a daily wear regimen by the patient. Furthermore, a small number of patients could wear this lens without interruption for 3 to 6 days at a time. Despite this good acceptance by patients, corneal problems (mainly staining) and lens problems (dry surfaces) were frequently encountered.

'Silicone rubber' has been used in tissue implants in the human for at least 20 years, mostly by plastic surgeons, and abundant references on their uses and adverse effects are available. As a contact lens the first patent was issued to Becker (1959), but it was only in the early 1970s that Mueller Welt (Black, 1972) in the USA and later Dow Corning made lenses available for investigation to use in human eyes. The original Dow Corning lenses, and the lenses manufactured by Titmus Eurocon (Giefer, 1977) and used in this study are surface coated in the form of a grafted hydrophilic surface. These differ from the material formulae (based on Siloxane) in the Volk and the Danker and Wohlk lenses. Furthermore, in all instances there are dissimilar lens designs. Therefore, while some conclusions will be concerned with silicone lenses in general, others will be for the specific lens used in this study.

Silicone rubber material interests the contact lens practitioner because of its possible higher gas permeability than any other material, but the in-vitro and in-vivo measurements by Simons *et al.* (1977), and Fitzgerald and Jones (1978) tended to show the latter are lower than expected. The coating process decreases the gas permeability, since it involves the use of non-silicone molecules. Although considered to be soft contact lenses, silicone rubber lenses are approximately 5 times more rigid than an equivalent 50% water content hydrophilic lens (Ruben, 1975).

The present study was carried out to assess the use of silicone rubber lenses in aphakia and to confirm the favourable impressions reported by Albarea *et al.* (1978), and Sundmacher (1978) as to their use as extended-wear lenses. The complications and adverse effects are also reported.

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Table 1 *Patients with previous contact lens experience*

Successful	Hard C/L	7	Soft C/L (DW)	2
Failure	Hard C/L	12	Soft C/L (DW)	6

Table 2 *Technical data on Tesicon lenses (from Giefer, 1977)*

O_2 permeability coefficient (in vitro)	$2{\cdot}75 \times 10^{-5}$ cm² per second
H_2O absorption	0·5%
Transparency	98%
Refractive index	1·423
Density at 25°C	1·07 g/cm³
Tensile strength	100%

Material and methods

Thirty-two aphakic patients (19 males and 13 females) aged 14 to 73 years (mean 50·2 years, SD 15·0 years) were fitted with silicone rubber lenses. These totalled 46 aphakic eyes with a mean keratometry of 7·82 mm (range 7·35 to 8·35 mm, SD 0·28 mm) and a mean difference in corneal radii 0·25 mm (range 0·00 to 1·00 mm, SD 0·19 mm). Of these 46 eyes 19 had never been fitted with contact lenses and were chosen at random, while the remaining 27 had previously worn contact lenses (Table 1).

The lenses used in this investigation were the silicone rubber lenses manufactured by Titmus Eurocon of Schaffenburg, West Germany. They were made of Tesicon, whose physical characteristics are given in Table 2. These lenses, as all silicone rubber lenses, are manufactured by a moulding process, and the range of fitting parameters available is limited. In the present study back optic radii (BOR) were available in 0·1-mm increments from 7·4 to 8·4 mm, the overall size (OS) was 12·7 mm, and the power range from −20·00 to +20·00 D. Some minus lenses were used to correct phakic eyes when uniocular aphakia was being treated.

The fitting philosphy was based on a trial lens approach after a complete prefitting ophthalmological investigation, when particular attention was given to aspects relevant to contact lens practice. During the biomicroscopic examination the tear break-up time (BUT) was recorded, and the central corneal thickness and visible iris diameter were measured. During our fitting we aim at the flattest possible lens which permits a centred fit. The trial lens of first choice was usually 0·3 mm flatter than the flattest keratometric value and with an OS of 12·7 mm and a power of +15·00 D. An over-refraction was performed after the lens with the correct fitting parameters had been worn for 1 hour.

The lenses were issued to the patients as daily-wear lenses with a recommended wearing time of 2 hours initially and an increase of 1 hour daily up to a maximum of 8 hours, the patients being seen after 1 week. Further follow-up visits were arranged at 1 month, 3 months, and then every 3 months for 1 year. Some successful patients were switched to extended wear protocol for periods of 3 to 7 days, with usually a control visit after 24 hours.

Results

The average follow-up time was 8·48 months (range 3 to 12 months) at the time of the survey. Thirty-four eyes (74%) were considered as successfully fitted. Criteria for successful fitting were taken from the patient's viewpoint—a minimum of 10 hours' comfortable daily wearing time. In the 12 other eyes (26%) either contact lens wear was abandoned (11 eyes) or 10 hours' wearing time could not be reached (1 eye).

Six patients were permitted to sleep with their lenses for periods of 3 to 6 days, and in all but 1 instance this was possible without problems of tolerance. But in most instances prolonged wear resulted in poor surface quality and punctate corneal staining with fluorescein. In 2 patients serious neovascularisation occurred and in 1 uveitis with stromal necrosis.

Table 3 *Causes for failure on daily wear*

Discomfort	4
Poor VA	5 (with dry spots)
Ulcer	2
Oedema	1
Total	12

The reasons for failures are recorded in Table 3. The commonest causes were discomfort and poor visual acuity (VA). The discomfort was conclusively linked to poor wetting surface in 1 case, while for the 3 others it seemed to be due to the small diameter of the lenses used; the edges impinge over the limbus with decentred lenses. The poor visual acuity was due to a poor wetting surface from the first day (3 eyes) and after 3 months (2 eyes) to surface deterioration.

Among the 34 eyes considered successful from the patients' viewpoint routine follow-up revealed various corneal problems, mainly corneal staining (10 eyes), new vessels (3 eyes), limbal indentation (5 eyes), oedema (1 eye). The corneal staining observed with Tesicon lenses is a punctate epithelial necrosis of the central cornea, more typical of hard contact lenses than soft contact lenses. New vessels were in most instances of the pannus type and in the superior quadrant, but 1 patient showed extensive new vessels after extended wear (Fig. 1). Limbal indentation was most obvious in 1 case of extended wear with a lens showing no movement at all, but 24 hours after contact lens removal no corneal staining was present.

The study of the lens surface showed dry spots in 11 cases (Fig. 2). These dry spots were linked to mucous deposits (8 cases) and/or cloudy lenses (4 cases). Therefore, despite the good acceptance of Tesicon lenses by aphakic patients, corneal problems, sometimes serious, are encountered.

The fitting characteristics of both successful and failed cases of daily wear were analysed and showed

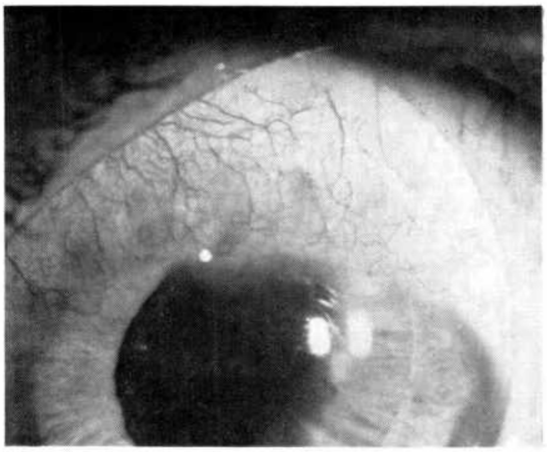

Fig. 1 *Gross pannus due to continuous wear of silicone rubber lens*

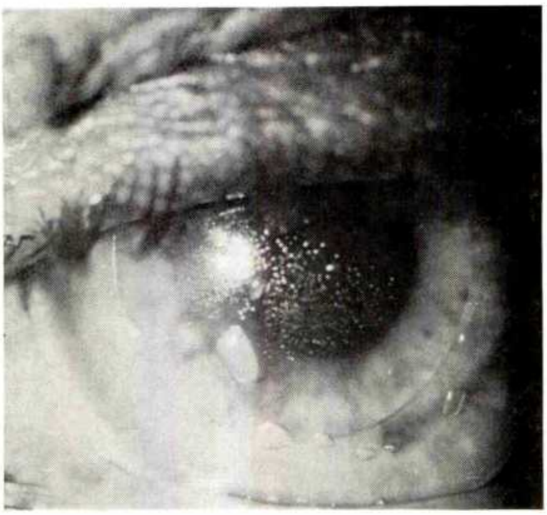

Fig. 2 *New silicone rubber lens showing mucous deposits and water droplets after half-hour wear*

that no systematic bias was introduced by using different fitting increments: the mean flattening was +0·35 mm for the successful group and +0·26 mm for the failure group. The difference was not statistically significant. These findings support the manufacturer's recommended trial lens choice.

Discussion

So far no extensive comparative studies involving Tesicon lenses have been published. However, the present work enables certain conclusions to be drawn.

Because of the limited number of parameters available it was not easy to obtain an accurate fitting. However, when the vision was less than expected, it was difficult to pinpoint the reason for this subnormal VA, whether of soft lens aetiology or because of poor surface quality.

In general, the lenses were well tolerated, particularly by wearers who had failed with hard contact lenses. Few patients could manage extended wear with these lenses, but no more than 3 to 4 days is advisable. When the lens was immobilised there was no corneal staining, which suggests that staining was traumatic in origin, hence a need for better wetting properties of the lenses manufactured in the future. In our opinion, the optimal silicone rubber lens should be a thin, small lens. A thin lens, particularly at the edge, would avoid limbal grooving induced by the high rigidity of this material, and a small lens minimises interference with the corneal metabolism.

The commonest problem encountered is that of dry spots. The pre-lens tear film is not continuous (Fig. 3). One remedy for this is to use contact lens solutions. On that point various approaches have been put forward: first soft-lens solutions were used, then specially formulated solutions were developed, neither with great success. Now the manufacturers recommend the use of hard-contact-lens solutions, which had been advocated for some time by Ruben (1978).

Because of the lens rigidity a posterior lens tear film is present between the lens and the cornea and collects mucus, as seen with hard scleral lenses.

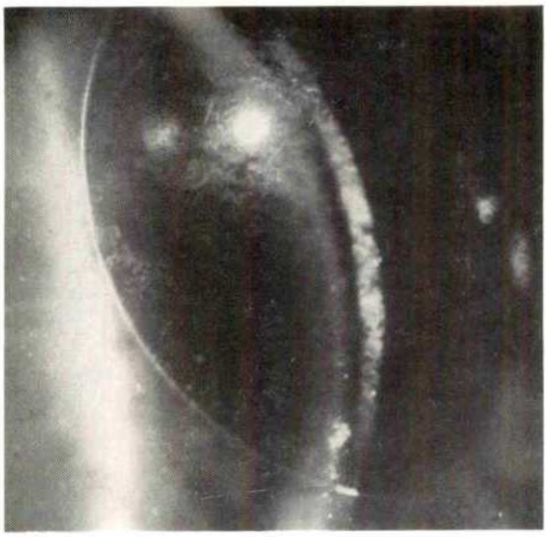

Fig. 3 *Typical drying of surface of silicone rubber when on the eye. Also showing corneo-lens tear space floating deposits*

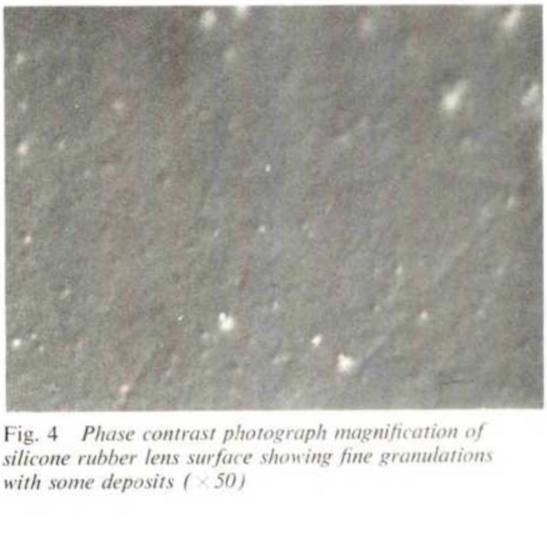

Fig. 4 *Phase contrast photograph magnification of silicone rubber lens surface showing fine granulations with some deposits (× 50)*

Deposits were present on both lens surfaces. It was therefore surprising to find few complications involving the palpebral conjunctiva. On the contrary, silicone rubber lenses were shown to create the most corneal staining in a study conducted by Hamano (1979), comparing hard corneal, daily, and extended wear hydrophilic and silicone rubber lenses. Recently, scanning electron microscopical observations by Hamano (1979) and contrast phase studies by Ruben and Guillon (1978) (Fig. 4) have shown the poor surface quality of the present silicone rubber lenses.

Finally, the deposits encountered on Tesicon lenses are not of the mulberry types but mucous, lipids, and foreign body materials in isolated areas. This suggests that with hydrophilic lenses degenerate polymer is present and causes some forms of deposit formation.

We thank the contact lens practitioners who at Moorfields Eye Hospital fitted some of the cases included in this study.

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Some clinically observed phenomena in extended contact lens wear

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SUMMARY Two groups of volunteer subjects wearing extended-wear soft lenses were monitored over a period of 20 weeks. Of 6 factors measured only 1, corneal touch threshold, was found to show evidence of progressive change. However, a high incidence of lens surface deposits was encountered.

The ocular response to contact lens wear may be manifested in a number of ways. In addition to corneal thickness changes, previously reported by the authors (Hirji and Larke, 1979), the eye may show evidence of change in corneal topography, corneal sensitivity, refractive state, visual acuity, corneal epithelial integrity, and the appearance of the palpebral conjunctiva covering the tarsal area of the upper lid. In a controlled comparative study, now reported, the foregoing factors were examined in 3 groups of persons over a period of 20 weeks.

Fifty-seven volunteer Caucasian persons who came within a previously described acceptance profile were randomly divided into 3 groups. The first group (the non-solution group) were fitted with a high-water-content soft lens (Sauflon 85, Contact Lens Mfg.). The second group (the solution users) were fitted with similar lenses, which were removed and cleaned at 8-week intervals with a proprietary cleaning agent (Monoclens C40, Contact Lens Mfg.). In addition they instilled 1 drop of proprietary sterile saline on waking (Salette, Contact Lens Mfg.) and before retiring each day. The third group retained their spectacles and acted as controls. Data were collected from the subjects before lens wear and at 4-week intervals until a period of 20 weeks had elapsed.

Results and discussion

CORNEAL TOPOGRAPHY

Corneal curvature was measured with the aid of a Zeiss keratometer and supplementary topogometer. Measurements were taken at the central region of the cornea and at 15° and 30° apparent angular subtense in the horizontal and vertical meridians. The collected data were subjected to multifactorial and multiple regression analysis, which showed no statistically significant change ($P<0{\cdot}001$) in shape occurring in any of the monitored regions. Corneal shape change invariably accompanies the wearing of hard traditional contact lenses (Rengstorff, 1965). However, with the advent of Hydrogel lenses no statistically significant curvature changes have been reported.

The results of this study on corneal shape changes in periods of extended contact lens wear indicated a similar response to that reported on daily Hydrogel lens wear. The very differing physical properties of hard and Hydrogel lenses, coupled with the evidence of corneal shape change in the former but not in the latter, may support the hypothesis that corneal shape change in contact lens wear is at least partly mechanical in origin.

CORNEAL TOUCH THRESHOLD LEVELS

Corneal touch threshold was measured with the aid of a Cochet and Bonnet aesthesiometer mounted in a moveable (X, Y) frame. Corneal touch threshold measurements were made in the vertical meridian, approximately 1 mm above the lower limbal margin of the cornea. A statistically significant change ($P<0{\cdot}001$) was observed in both groups of contact lens-wearing subjects. In addition a statistically significant difference ($P<0{\cdot}001$) was also observed between these 2 groups of subjects.

The collected data subjected to multiple regression analysis are graphically illustrated along with the regression equations in Fig. 1. It is apparent from Fig. 1 that the corneal touch threshold increased progressively throughout the 20-week period of the study. At the end of about 12 weeks the reduction

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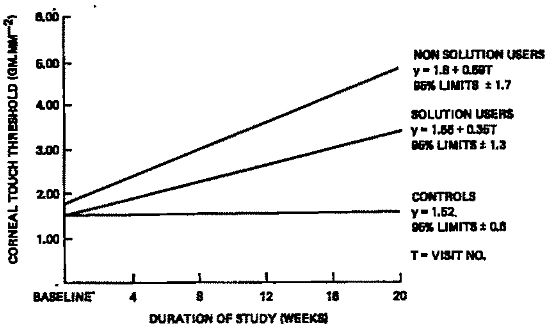

Fig. 1 *Corneal touch threshold over 20 weeks of extended contact lens wear*

in sensibility level is approximately equivalent to that which would have been achieved in about 1 day of traditional hard contact lens wear (Millodot, 1976). The difference between the 2 groups is not clearly understood at present. The lenses worn by both groups of participating subjects became covered with deposits as the study progressed. It is possible that the presence of these deposits contributed to the reduction in corneal sensibility. Among the group of patients who used proprietary solutions to clean the lenses the reduction in sensibility levels was less than among those who did not (though it should be borne in mind that the cleaning procedures allowed some corneal recovery time in this group of patients). However, this is only a tentative conclusion at present in view of the possibility that corneal touch threshold levels may also reflect subtle physiological changes occurring in the cornea.

REFRACTIVE STATE

Conventional refraction techniques were used to carry out over-refraction on the persons wearing contact lenses during the 20 weeks of the study. Multivariant regression analysis did not show a statistically significant change in this factor.

Although the ocular refraction without contact lenses in these groups of persons was not monitored in this study, in the absence of significant changes of over-refraction and corneal surface topography it is very unlikely that clinically significant changes in the ocular refraction over the duration of the study were in fact present and undetected. This strongly suggests a stable refractive pattern for this type of contact lens wear for the duration of the study.

VISUAL ACUITY

The visual acuity of the 3 groups of participating subjects was assessed on a conventional internally illuminated letter chart. The results showed no statistically significant evidence of change in the data over the study period nor between the 3 groups. However, empirical inspection of the data suggested some fluctuation, and, in particular, the standard deviation for the 2 groups of contact lens-wearing subjects appeared to be greater than that for the control subjects (Fig. 2). Such an interpretation was further supported by subjective comments by the patients of the appearance of 'watery' or somewhat unstable vision during the progress of the study. However, it is interesting to note that, although the contact lenses were subject to significant levels of deposits, this did not result in an associated depressed level of visual acuity for the group as a whole.

EPITHELIAL INTEGRITY

Epithelial integrity was assessed before and after contact lens wear with the aid of 1% sodium fluorescein and 2% rose Bengal, the eyes being examined by a slit lamp. An eyepiece graticule was used to assess the area of any staining observed during examination. It was found possible in almost all patients to find evidence of isolated punctate stain using either rose Bengal or fluorescein occupying less than 2% of the corneal surface on almost all the occasions on which the patients were examined. The writers regard this level of staining as a reflection of the 'normal' level of staining in patients at examining times. The incidence of vital staining involving more than 2% of the corneal surface was found not to differ ($P < 0{\cdot}001$) between the groups or between the periods of examination. Hence no evidence of epithelial trauma was detected in the present study.

APPEARANCE OF PALPEBRAL CONJUNCTIVA

On completion of 20 weeks of extended contact lens wear the upper lids of all participating subjects were everted for an examination for the presence of giant conjunctival papillae. One instance of giant papillae in excess of 1 mm in diameter was encountered, while 5 instances of small raised (cobblestone) areas

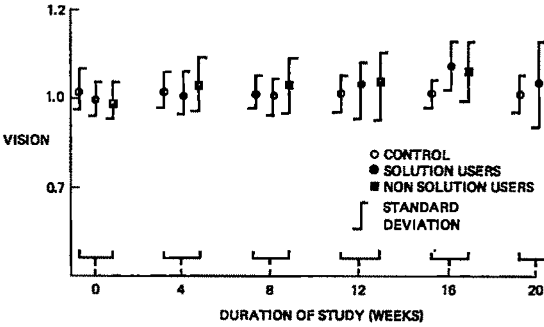

Fig. 2 *Vision over 20 weeks of extended contact lens wear*

Table 1 *Incidence and type of deposits*

Incidence (%) in week number				
4	**8**	**12**	**16**	**20**
29	39	50	63	55

Type	%
Crystalline	10·8
Film-like	7·4
Granular	12·7
Speckles	7·4
Others	8·9

were noted. The appearance of giant conjunctival papillae is in all aspects similar to that first reported by Allensmith *et al.* (1977), and we have no further comments to add to those already reported in the literature.

COMPLICATIONS

In addition to the factors already disussed two further features arose in the study which we came to regard as complications of extended lens wear. The first was the high incidence of deposits on the lenses, and the second was a single instance of suspected growth of blood vessels into the cornea.

Deposits on soft contact lenses have been widely reported. In the present case the deposits had an apparently characteristic discrete appearance and were readily observed with the aid of a slit lamp by retroillumination. A record was kept of the incidence of deposits, and the results are summarised in Table 1. It is of interest to note that patients whose lenses were cleaned at 8-week intervals were still subject to a high level of deposits. It would seem wise for the efficacy and frequency of use of the cleaning compound used in this study to be closely examined.

During the course of the study the limbal arcades of one participating subject became congested. At the 12th week of wear an apparently unbranched and non-returning arcade was observed in the lower nasal quadrant of the left eye. The patient was advised to cease lens wear and was observed for a further 4 weeks. The eye became clear in less than 1 day, and no further problems were encountered. The subject was not allowed to resume lens wear.

Conclusions

The progressive increase in the corneal touch threshold of the contact lens-wearing subjects was the only factor monitored in this study to show evidence of progressive change. The loss in sensibility is approximately equivalent to what would be observed after 1 day's wear of hard contact lenses, though it is not possible to determine if the raised threshold is essentially mechanical or physiological in origin.

The very high incidence of lens surface deposits encountered among lens wearers is a serious complication to lens wear. The appearance of changes in the palpebral conjunctiva which Allensmith *et al.* (1977) has shown to arise from surface deposits strongly suggests that this problem requires to be resolved before extended lens wear becomes a practical proposition. Should a remedy to surface deposits be found, the nature of the ocular response to extended contact lens wear found in the present study suggests that such lenses are generally acceptable to the eye, at least in the short term.

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Endothelial bedewing of the cornea in association with contact lens wear*

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SUMMARY Endothelial bedewing is described as either a cluster of oedematous droplets or a constellation of leucocytes deposited on the surface of the corneal endothelium. The use of marginal retroillumination in biomicroscopy is described for the detection of endothelial bedewing. Some of the clinical characteristics of endothelial bedewing are outlined, and its occurrence in patients who are chronically intolerant to contact lens wear is reported. For these intolerant individuals endothelial bedewing may be indicative of a limited anterior uveal response associated with contact lens wear.

The early use of biomicroscopy to observe the ocular response to contact lens wear, emphasised an evaluation of superficial corneal integrity, with oedema and fluorescein staining as the chief criteria for assessment. In recent contact lens work there has been increased interest in the deeper corneal layers with the observation of vertical striae in oedematous stroma (Sarver, 1971).

Deeper still into the cornea the endothelium has received increased attention in biomicroscopy, with the observation of rapid, reversible changes in the appearance of the endothelial mosaic in association with contact lens wear (Zantos and Holden, 1977). However, the possibility of the effects of contact lens wear being manifest posterior to the endothelium has received scant attention, though it is interesting to note that a converse association has been reported. Goldberg (1970) observed that patients with posterior corneal coloured precipitates, when fitted with corneal contact lenses, suffered various forms of corneal interference and symptoms resembling overwear of contact lenses, despite only short wearing times.

The purpose of this paper is to report the observation of endothelial bedewing in some patients who show a chronic intolerance to contact lens wear. Endothelial bedewing is not a clear clinical entity in relation to non-wearers of contact lenses, and its occurrence in association with contact lens wear has not previously been reported.

Stocker (1971) states that endothelial bedewing may be produced either by oedema of the endothelial cells or by precipitation of small particles of inflammatory material on the posterior surface of the cornea. In the latter case these particles include leucocytes which have been circulating in the anterior chamber (Heydt, 1923). Such cellular keratic precipitates (KP) are regarded as physiological if the cells show amoeboid movement and no tendency towards agglutination and are frequently seen in otherwise normal eyes, especially in children and adolescents (Duke-Elder, 1965). In pathological conditions such as uveitis Duke-Elder states that the deposition of KP, including leucocytes, is usually preceded by oedematous changes in the endothelium (bedewing). Thus the two forms of bedewing (oedematous and cellular) need not occur as separate clinical entities.

The classification of endothelial bedewing as either physiological or pathological may not be easy in clinical practice. However, such differentiation may be important when assessing the clinical significance of endothelial bedewing in contact lens practice, when it may be evident as a pre- or post-wear sign.

Materials and methods

By means of the slit-lamp biomicroscope with the illumination system at about 45 degrees to the observation axis, and a slit beam of 0·5 to 1·5 mm

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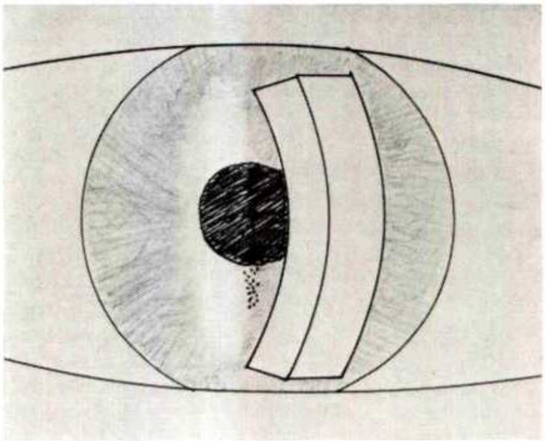

Fig. 1 *Schematic representation of endothelial bedewing in the region of Ehrlich-Turk formations as seen by marginal retroillumination*

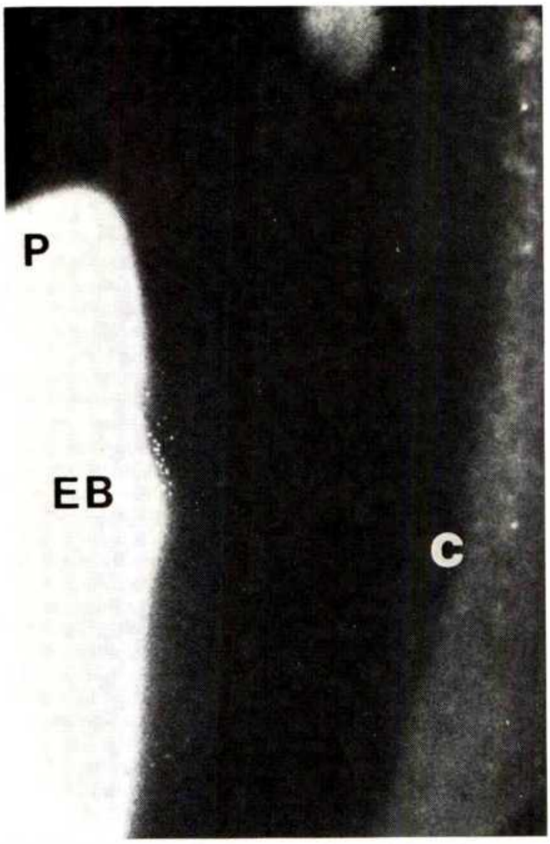

Fig. 2 *Endothelial bedewing (EB) consisting of some 20 to 30 particles. The inferior margin of the pupil (P) and the anterior face of the corneal parallelopiped (C) are shown. Magnification of the original slide was ×7·8*

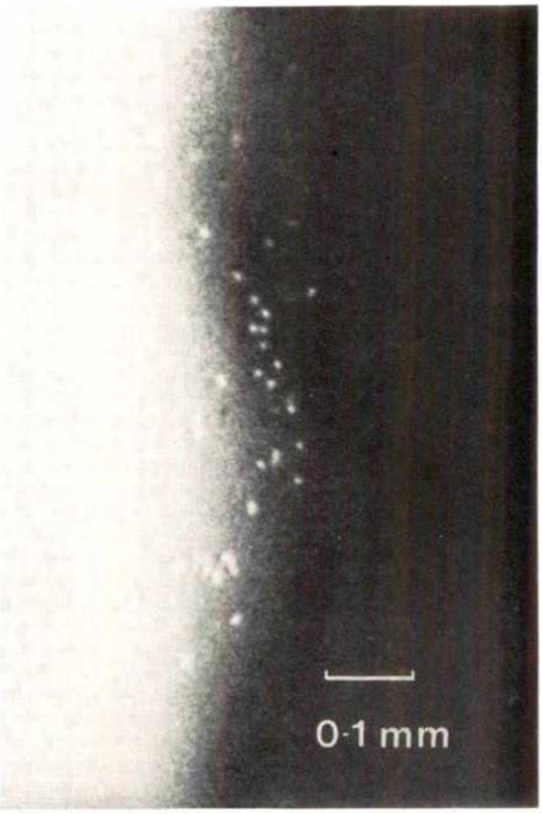

Fig. 3 *Enlargement 3·4 times of Fig. 2, showing the particles of endothelial bedewing*

width, the endothelial bedewing can be detected with retroillumination from the iris at magnifications of 20 times or more. The observation is carried out in the region of the cornea in line with the inferior pupil margin (the area of Ehrlich-Turk formations), with the observer's attention focused on the very edge of the beam reflected from the iris. In this critical position the droplets or white cells will be illuminated by the light reflected from the iris, and contrasted against the non-illuminated part of the iris (Figs. 1 and 2). This technique is termed marginal retroillumination (Graves, 1924), as it lies exactly between the techniques of direct and indirect retroillumination in slit-lamp biomicroscopy. The non-movement of bedewing particles contrasted with the movement of particles in the tear film following a blink is an aid in detection, but excess tear mucoid interferes with detection and observation, more so with the contact lens in situ.

In this report photographs were taken with a Nikon zoom photo slit lamp and a high magnification photographic technique described by Holden and Zantos (1977). Kodachrome 64 film was used for the original photographs (Fig. 2).

Results

Over a 9-month period endothelial bedewing was detected and carefully monitored in 25 patients who had either experienced marked difficulty in adapting to contact lenses or who had shown a marked loss of tolerance after a period of successful contact lens wear. These 25 patients formed a diverse group, ranging in age from 14 to 39 years (mean 27 years), with a female:male ratio of approximately 2:1. With the exception of one hard-lens wearer all wore or had attempted to wear soft contact lenses.

All cases of endothelial bedewing observed by the authors were detected in the region of the inferior central cornea near to or immediately below the inferior margin of the pupil. The area of bedewing varied in shape from a discrete oval cluster of particles to a less discrete, more or less dispersed Ehrlich-Turk formation. When initially detected the number of particles in the formation was found (by estimation) to vary between 20 and 50. In some cases subsequent observation days or weeks after the first would reveal that there had been a gradual dispersion of the particles, resulting in a formation that appeared to contain fewer particles. The change in the appearance of the endothelial bedewing with time varied from patient to patient. In some cases the bedewing completely disappeared within 3 to 4 months, while in other cases it changed little over many months.

The following case reports are representative of the authors' experience.

CASE 1

This patient, an unmarried woman of 25, began experiencing gradual loss of tolerance to her hard (PMMA) contact lenses after 5 years' successful wear. Three months after having abandoned wearing these lenses she reported for examination. Biomicroscopy revealed clear corneae and an absence of endothelial bedewing. Soft (Hema) contact lenses were supplied. These fitted well, but gave only 3 hours' tolerance after 2 weeks of attempted adaptation. Examination showed bilateral marked conjunctival injection with mild epithelial erosion in the right eye and endothelial bedewing in the left. There was no aqueous flare. After 1 week's abstinence from lens wear (during which time the lenses were altered to increase tear circulation), endothelial bedewing was now detected in both eyes, which otherwise appeared normal. Further restricted lens wear was attempted, but with limited success. A change-over from heat to chemical disinfection of the contact lenses brought no significant improvement in tolerance. Gradually over the next 2 months the bedewing resolved, but tolerance to lens wear did not exceed 5 hours.

CASE 2

This patient, a married woman of 34, had been fitted with extended-wear hydrophilic contact lenses (Permalens), which were worn for 17 months without difficulty. She first reported for examination when marked symptoms of intolerance occurred, necessitating the removal of the contact lenses. These difficulties had been preceded by an unaccustomed fogging of vision, which had increased in intensity over the few days prior to lens removal. Examination revealed bilateral marked epithelial oedema which obscured the deeper corneal layers. Six days later the corneae were clearer, and endothelial bedewing was detected in both eyes. Over the next 2 months attempts to wear contact lenses caused sufficient symptoms to restrict usage to an occassional 2 to 3 hours' wear. The only corneal abnormality that was observed over this period was a gradual dispersion of the endothelial bedewing. Four months later minor bedewing persisted in both eyes, and contact lens wear was limited to 6 hours.

CASE 3

This patient, an unmarried woman of 39, had had 10 years' trouble-free wear of hard (PMMA) contact lenses, when she experienced a typical overwear syndrome after the use of the lenses for 3 hours more than her usual 12 hours' wearing time. She abstained from lens wear and presented for examination 3 days later. Both eyes showed slight loss of normal corneal transparency and the presence of endothelial bedewing in cluster form in the right eye and a well dispersed constellation in the left eye. After a further 1 week's abstinence from lens wear the right eye showed a partly dispersed Ehrlich-Turk formation, and the left eye a few cells only. Attempts to wear the lenses during the next week were accompanied by an unaccustomed stinging that limited wear to 5 difficult hours. A few days later the patient reported a recurrence of overwear symptoms, though the recommended wearing period had not been exceeded. This case is still being followed up.

Discussion

The explanation for the coincidence of chronic intolerance to contact lens wear and endothelial bedewing can only be a matter of speculation at this stage. However, it is possible that, because the corneal endothelium and the anterior uvea form an intimate continuum, a disturbance to the cornea following contact lens wear may be accompanied by a response from the anterior uvea. The presence of inflammatory cells in the aqueous is a result of leakage through uveal blood vessels, a process which accompanies disturbances to the surrounding tissues. The subsequent deposition of cells on the corneal posterior surface is largely dependent on the thermal circulation of the aqueous and on changes in the endothelial cells predisposing to the adherence of precipitates.

According to this explanation, therefore, whenever corneal oedema occurs as a result of chronic or acute overwear of contact lenses there exists the possibility of an associated uveal response in the form of cellular escape into the aqueous. Recovery of the eye may take longer than the few days required for the disappearance of the usual clinical symptoms and signs of corneal oedema. The patients reported in this paper have shown a persistence of endothelial bedewing and concomitant reduced tolerance to contact lenses with subsequent attempts at wear. It has been a clinical experience of the authors to note intolerance to contact lenses lasting weeks or months after an episode of corneal oedema due to lens overwear. This prolonged intolerance suggests that the eyes had not completely recovered from the trauma of overwear, though normal corneal transparency had been regained. These cases have been remembered because of the difficulty in explaining to the patient the facts of good contact lens tolerance before the episode of overwear.

The apparently high incidence of endothelial bedewing in the special class of patients that suffer chronic intolerance to contact lens wear has been found to be in contrast with the incidence of endothelial bedewing in both prospective contact lens wearers and successful (non-intolerant) contact lens wearers. No cases of endothelial bedewing were found in a group of 25 prospective contact lens wearers who reported consecutively for examination, while 2 cases of bedewing have been observed in successful wearers.

The relationship between endothelial bedewing and intolerance to contact lens wear appears not to be obligatory, since the 2 conditions do not necessarily occur together. This is evidenced by the fact that not all intolerant lens wearers show endothelial bedewing and also by the occasional observation of endothelial bedewing in successful contact lens wearers. It would seem also that intolerance to contact lens wear and endothelial bedewing need not follow the same time course. In some cases the intolerance (though to a lesser degree) has persisted for weeks or months after the disappearance of the endothelial bedewing.

Conclusion

It is proposed that endothelial bedewing may result from an overt corneal oedema response associated with contact lens wear. The presence of endothelial bedewing may be an indication that the eye has not fully recovered from the episode of oedema, that the endothelium is still compromised, and that the prospects for successful contact lens wear are reduced. Thus it is possible that endothelial bedewing may be associated with, and an indication of, a limited uveal response to contact lens wear.

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An improved diagnostic contact lens

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SUMMARY Modification of a standard Goldmann goniolens by reducing the curvature of the contact surface to 8·5 mm radius of curvature (from the standard curvature of 7·4 mm) enabled gonioscopy to be carried out without the nuisance of air bubbles.

One of the principal difficulties encountered in the use of diagnostic contact lenses is the presence of a central air bubble. This can be largely avoided by filling the lens with a solution of 1 or 2% hydroxypropyl methyl cellulose (HPMC) made up in 0·8% sodium chloride instead of water to avoid corneal oedema (Smith and Watkins, 1976).

Experience with the Zeis 4 mirror goniolens showed that a smaller corneal segment with a flatter curve tended to eliminate the central air bubble without the need of Methocel, and it was then decided to try modifying a normal Goldmann single mirror goniolens by working a flatter corneal curve.

An old goniolens (with scleral rim) was therefore cut down. The rim was removed, and the corneal contact surface was ground and polished to a single curve of 8·5 mm radius of curvature (the standard lens has a curvature of 7·4 mm) (Fig. 1). The effect on gonioscopy and central fundus examination is dramatic. All that is now needed (after anaesthetising the cornea with a drop of benoxinate 0·4%) is simply to put the lens against the cornea while the patient is seated with the head in the full slit-lamp position, that is, not held back from the chin and head-rest but forward ready for examination. No fluid of any sort has to be added, though a single drop of saline or Methocell can be put on the lens surface if there is a suspicion of an inadequate tear film. In practice, however, this is normally unnecessary. When the lens is placed in position it needs to be lightly held in the normal way, but if released it is more likely to fall out than formerly. The view obtained is of a central air-free zone with wrinkling of Descemet's membrane if much pressure is exerted. The tear film makes an efficient optical bond in the central cornea and a thin peripheral air bubble shifts about as the lens is manipulated. The peripheral bubble does not interfere with the gonioscopic or central fundus view unless the lens is so tilted by the observer as to allow it to do so.

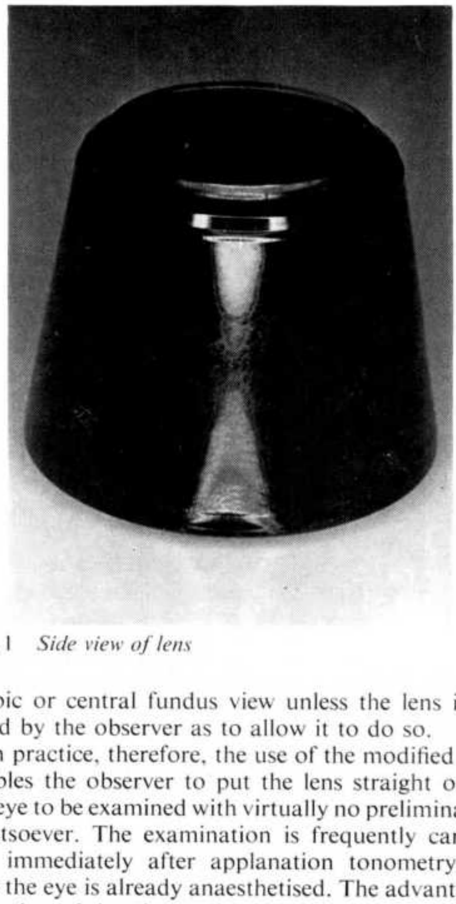

Fig. 1 *Side view of lens*

In practice, therefore, the use of the modified lens enables the observer to put the lens straight on to the eye to be examined with virtually no preliminaries whatsoever. The examination is frequently carried out immediately after applanation tonometry, so that the eye is already anaesthetised. The advantages in saving of time in application, independence from a supply of methyl cellulose, and avoidance of the air bubble nuisance are obvious.

Another occasion on which the lens may be invaluable is in the examination of the prone patient in the operating theatre with an operating microscope. Air bubbles and the need to avoid methyl

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cellulose just before possible surgery have meant that the Goldmann contact lens has had hitherto a very limited application in the operating theatre. This is not the case with the improved lens, which can be freely used in routine examinations under anaesthetic for congenital glaucoma.

My thanks are due to Mr Montague Ruben, of the Contact Lens Department, Moorfields Eye Hospital, for valuable advice and practical assistance in the production of the modified goniolens; the Contact Lens Department at Moorfields Eye Hospital for making the modifications; to Miss S. Ford, of the Western Ophthalmic Hospital, for the photograph; and to Miss J. Quaife for secretarial assistance.

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Visual loss and foveal lesions in Usher's syndrome

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SUMMARY Forty-eight patients with Usher's syndrome were assessed for the degree of visual loss, extent of lens opacities, and presence of foveal lesions. Twenty-one patients (44%) showed either atrophic or cystic-appearing bilateral foveal changes. Despite having foveal lesions and variable degrees of lens opacities most patients maintained central visual acuity of 20/60 or better until their middle 30s.

von Graefe (1858) was first to report the association of retinitis pigmentosa and congenital hearing loss. Subsequent reports, including those by Usher (1914) and Hallgren (1959), emphasised additional though variable findings that include cataracts, speech disorder, mental retardation, psychosis, and vestibular ataxia.

Although isolated reports refer to loss of central vision with increasing age in patients with Usher's syndrome (Merin *et al.*, 1974; Bergsma, 1976; Abraham *et al.*, 1977), actuarial data documenting progressive visual loss and quantitative analyses of contributing factors (for example, foveal lesions and cataracts) are not, to our knowledge, available in the ophthalmic literature.

This study analyses loss of central vision in patients with Usher's syndrome and correlates changes within the lens and fovea with the degree of central visual loss.

Patients and methods

Forty-eight consecutive patients with Usher's syndrome were prospectively examined and included in this study. All patients complained to some degree of nyctalopia and all showed abnormal rod function by electroretinography. The majority had bone-spicule-like pigmentary changes within the retina. Although it varied in severity, all the patients had some congenital deficiency of neurosensory hearing.

Each patient underwent a careful fundus examination with emphasis on slit-lamp contact lens and direct and indirect ophthalmoscopy. Lens changes were assessed by slit-lamp biomicroscopy and categorised as to the presence and degree of posterior subcapsular lens opacities by criteria shown in Fig. 1. Qualitative categorisation of foveal changes was accomplished by using previously published descriptions of the types of foveal lesions seen in patients with retinitis pigmentosa (Fishman *et al.*, 1977a, b). Fluorescein angiograms were obtained by standard procedures following the rapid injection of 5 ml of

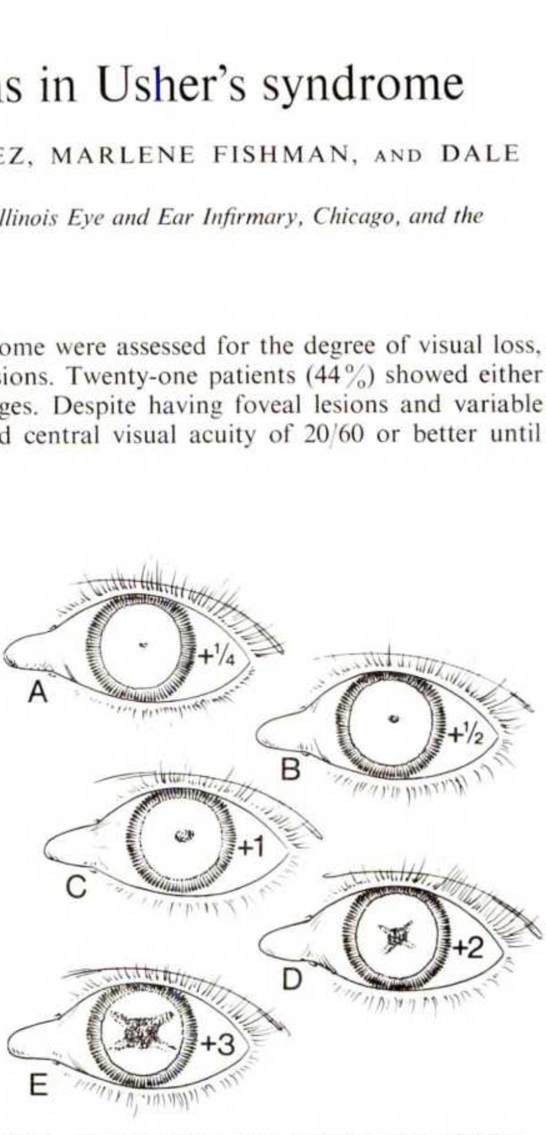

Fig. 1 *Degrees of increasing posterior subcapsular lens opacities (A–E)*

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10% sodium fluorescein into an antecubital vein. In addition all patients had colour fundus photographs and a cycloplegic refraction to obtain the best corrected visual acuity.

Results

Table 1 shows the age, sex, vision, extent of lens changes, and type of foveal lesion seen in the 48 patients. The fovea is defined here as a 1·5-mm area within the macula that projects approximately 6° on central visual field testing with the foveola at its centre. We define the macula as an area of approximately 5 mm in diameter that projects perimetrically 16° to 20° of the central visual field.

Table 1 *Patient data and clinical findings**

Patient No.	*Age (yr)*	*Sex*	*Fovea*		*Lens*		*Vision*	
			OD	*OS*	*OD*	*OS*	*OD*	*OS*
1	26	F	A	A	$+\frac{1}{4}$	$+\frac{1}{4}$	20/50 − 2	20/40 − 1
2	21	F	NL	NL	N	N	20/30 − 2	20/30 + 2
3	19	F	CME	CME	N	N	20/25 + 2	20/25 − 2
4	36	F	NL	NL	$+\frac{1}{4}$	$+\frac{1}{4}$	20/30 + 2	20/20 − 2
5	23	M	NL	NL	+1	+1	20/30 + 3	20/30 + 2
6	26	F	A	A	$+\frac{1}{2}$	$+\frac{1}{4}$	20/30 + 2	20/30 + 2
7	50	M	NL	NL	APH	APH	20/30 − 1	20/40 − 1
8	28	M	NL	NL	$+\frac{1}{4}$	$+\frac{1}{4}$	20/30	20/30
9	37	M	A	A	+1	+1	20/80 + 2	20/200
10	47	F	CME	CME	+3	+2	20/400	20/60 − 2
11	12	F	NL	NL	N	N	20/40 − 1	20/40 − 1
12	14	F	CME	CME	N	N	20/30	20/30 − 2
13	32	F	NL	NL	$+\frac{1}{4}$	$+\frac{1}{4}$	20/25 + 2	20/25 + 1
14	69	M	A	A	APH	APH	HM	HM
15	21	M	NL	NL	N	N	20/30 + 2	20/30 + 2
16	19	F	A	A	N	N	20/60	20/100
17	28	F	NL	NL	+1	+1	20/25 − 2	20/25 − 2
18	31	M	NL	NL	N	N	20/20	20/20
19	22	F	NL	NL	N	N	20/30 + 3	20/30 + 2
20	51	M	CME	CME	+2	+2	20/50	20/70 − 1
21	20	M	CAP	CAP	N	N	20/50 − 1	20/60 − 2
22	27	F	NL	NL	N	N	20/20 − 2	20/20 − 1
23	21	M	NL	NL	N	N	20/20 − 1	20/20 − 1
24	23	F	NL	NL	N	N	20/30	20/25
25	13	F	A	A	N	N	20/70 + 2	20/60
26	10	F	NL	NL	N	N	20/20 − 2	20/25 + 2
27	22	M	NL	NL	N	N	20/50 − 2	20/50 − 1
28	25	M	NL	NL	$+\frac{1}{4}$	$+\frac{1}{4}$	20/30 − 2	20/30
29	49	F	A	A	+2	+2	20/400	20/400
30	48	F	A	A	+1	+1	20/400	20/400
31	35	M	NL	NL	+2	+2	20/50 + 2	20/60 − 1
32	24	M	NL	NL	N	N	20/25 − 2	20/20
33	36	F	A	A	+1	+1	20/70 + 1	20/60 + 2
34	52	F	A	A	+2	+2	20/400	20/400
35	17	F	CME	CME	N	N	20/25 − 1	20/25 + 2
36	33	F	A	A	+2	+1	20/40 − 1	20/40
37	30	F	NL	NL	N	N	20/20 − 1	20/20
38	31	F	NL	NL	$+\frac{1}{4}$	$+\frac{1}{4}$	20/20 − 2	20/20 − 2
39	17	F	CME	CME	N	N	20/30 − 2	20/30 − 2
40	13	F	NL	NL	N	N	20/30	20/30
41	19	F	NL	NL	N	N	20/20	20/20 − 2
42	21	F	NL	NL	N	N	20/25 − 1	20/20 − 2
43	34	M	A	A	+1	+1	20/400	6/200
44	35	M	A	A	+2	+2	20/200	20/200
45	26	F	NL	NL	N	N	20/25	20/20
46	20	F	NL	NL	N	N	20/20	20/25
47	23	F	NL	NL	$+\frac{1}{2}$	$+\frac{1}{4}$	20/50 − 2	20/30 − 2
48	61	M	A	A	+2	+2	10/400	LP

*A indicates atrophic-appearing lesion; NL, no foveal lesion; CME, cystoid macular oedema; CAP, cystic-appearing foveal lesion; N, no lens opacity; APH, aphakic; HM, hand motions; and LP, light perception

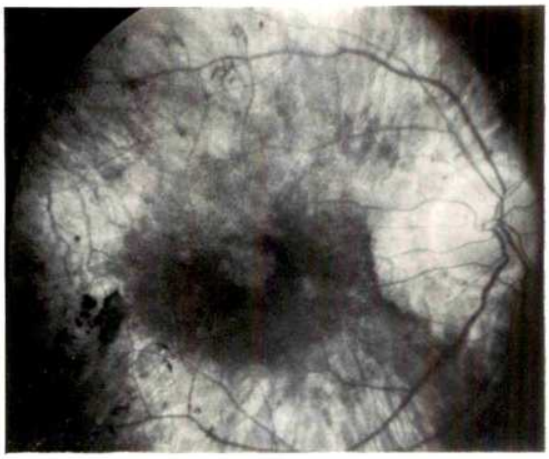

Fig. 2 *Atrophic-appearing foveal lesion in the right eye of patient with Usher's syndrome*

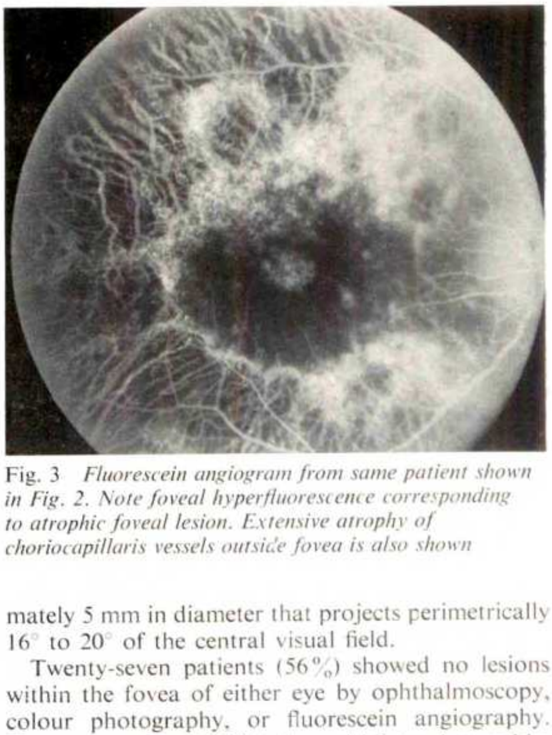

Fig. 3 *Fluorescein angiogram from same patient shown in Fig. 2. Note foveal hyperfluorescence corresponding to atrophic foveal lesion. Extensive atrophy of choriocapillaris vessels outside fovea is also shown*

Twenty-seven patients (56%) showed no lesions within the fovea of either eye by ophthalmoscopy, colour photography, or fluorescein angiography. Fourteen patients (29%) showed bilateral atrophic-appearing foveal lesions, as noted in Figs. 2 and 3. The atrophic foveal changes in 5 of these 14 patients were subtle, being convincingly apparent only on slit-lamp contact lens examination and fluorescein angiography. An atrophic-appearing foveal change was, with two exceptions, accompanied by a significant degree of reduction in central acuity. Two patients (1 and 6) with subtle atrophic-appear-

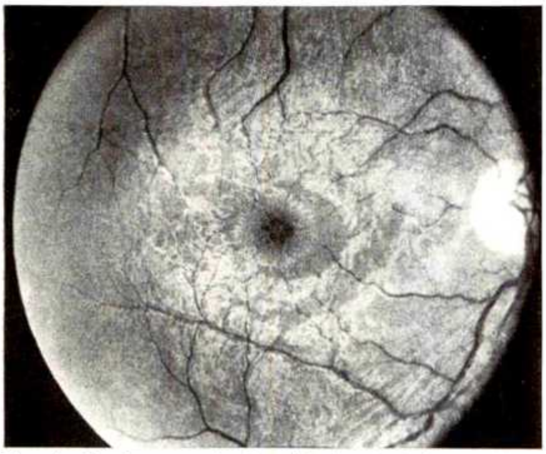

Fig. 4 *Cystic-appearing foveal lesions in right eye. Note extensive shimmering appearance of perifoveal region associated with changes of internal limiting membrane*

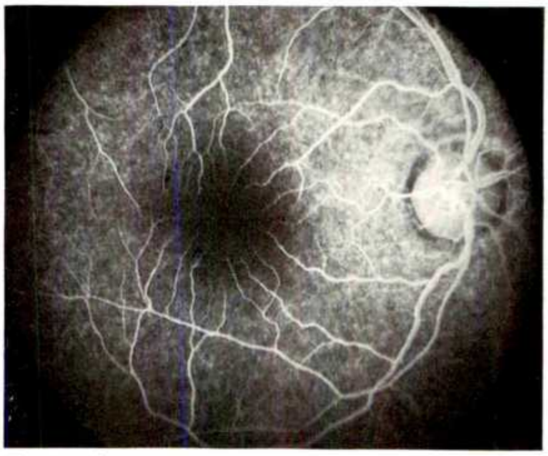

Fig. 5 *Fluorescein angiogram from patient shown in Fig. 4. No fluorescein dye leaks from perifoveal retinal capillaries*

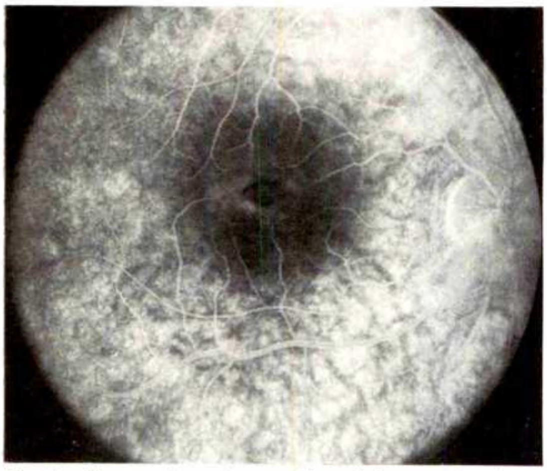

Fig. 6 *Fluorescein angiogram from right eye of patient with cystoid macular oedema. Note leakage from perifoveal capillaries*

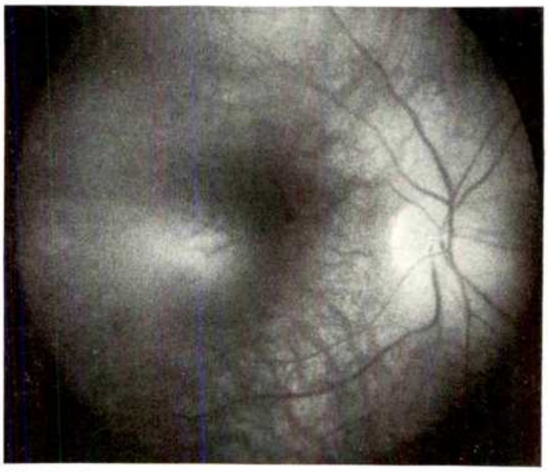

Fig. 7 *Late stage angiogram from same patient shown in Fig. 6. Note accumulation of dye within cystoid spaces. Black spot in centre of photograph is artefact*

ing foveal lesions showed central visual acuities between 20/30 and 20/50 in each eye. These patients did not, however, show atrophic changes directly within the foveola but rather towards the margin of the fovea. The remaining 12 patients showed atrophic-appearing changes that involved the foveola, and they had visual acuities of 20/60 or less in each eye.

One patient (2%) showed bilateral cystic-appearing foveal lesions that were not associated with leakage of fluorescein dye from perifoveal capillaries on angiography (Figs. 4 and 5). Since an intact internal limiting membrane was not evident on slit-lamp biomicroscopy, these cystic-appearing lesions would most accurately be classified as partial-thickness holes. Even in the absence of lens changes visual acuity was reduced to 20/50 and 20/60 in the right and left eyes, respectively. Six additional patients (13%) showed cystic-appearing lesions accompanied by leakage from perifoveal retinal capillaries. In 4 of the 6 patients the cystic changes were subtle enough to be missed on superficial examination by direct ophthalmoscopy and were only suspected by contact lens examination and subsequently confirmed by fluorescein angiography (Figs. 6 and 7). In the absence of lens opacities in 4 of these 6

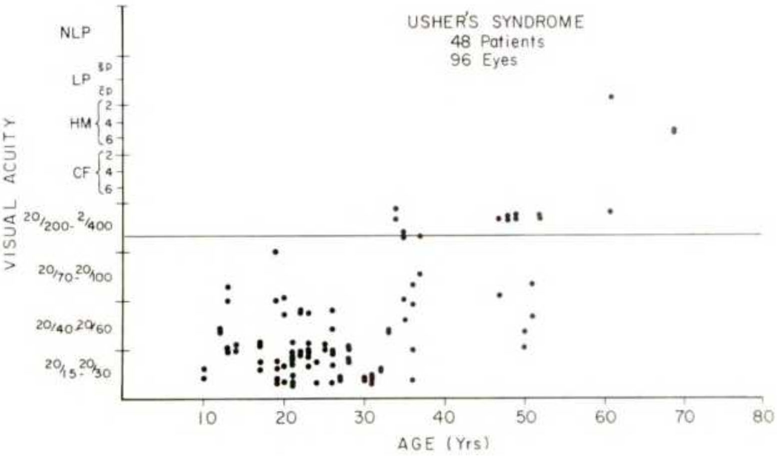

Fig. 8 *Scattergram showing degree of visual loss with age in 48 patients with Usher's syndrome. The numbers 2, 4, and 6 represent distance in inches. Symbols* $\bar{c}p$ *and* $\bar{s}p$ *indicate with and without correction, respectively. Horizontal line shows 20/200 level of central acuity*

patients the presence of cystoid macular oedema did not compromise central visual acuity to levels below 20/30.

The degree of visual loss with age is plotted in Fig. 8. Central visual acuity to 20/60 or better is retained in the majority of patients until the mid-30s. Although enough representative cases are not available beyond the age of 40 years, there is a trend toward a significant reduction in central acuity to levels of 20/200 or less. Note, however, that in 3 patients (5 eyes), central acuity of 20/70 or better was evident until the early 50s. Until age 40 only 5 of 82 eyes showed visual loss of 20/200 or less, while beyond that age 11 of 16 eyes showed a loss to levels of 20/200 or less.

Lens changes are recorded in Table 1. Not unexpectedly there was a trend toward increasing degrees of lens opacities with age. The degree to which lens opacities compromised visual acuity in individual patients could not be assessed with any reliable degree of accuracy. Nevertheless, with appropriate cataract surgery, it is likely that the potential for visual performance, as depicted in Fig. 8, is somewhat better than actually represented because of the influence of posterior subcapsular lens opacities.

Discussion

An atrophic-appearing foveal lesion is the most frequently found fundus alteration associated with significant loss of central visual acuity in patients with Usher's syndrome. If the atrophic changes spare the foveola, less extensive loss in central acuity occurs. Additionally, a less frequent finding that is associated with at least a moderate reduction in central acuity is partial-thickness foveal holes. In our patients the presence of cystoid macular oedema did not compromise central acuity beyond the level of 20/30 when posterior subcapsular lens opacities were absent.

As a general finding patients with milder degrees of foveal pigment atrophy that spared the foveola tended to show either no or less-extensive (+1 or less; Table 1) posterior subcapsular lens opacities. When grossly apparent atrophic-appearing foveal lesions with foveolar involvement were found, the degree of lens changes were generally more extensive (+2 or greater; Table 1). These latter patients were, as a group, older than those with less extensive atrophic-appearing foveal lesions and less-extensive lens opacities. Four of the 6 patients with cystoid macular oedema were less than 20 years old and showed no clinical evidence of posterior subcapsular lens opacities. The other 2 patients were 47 years and 51 years, respectively, and both showed extensive (+2 or greater) posterior subcapsular cataractous changes.

The data shown in Fig. 8, which depict visual loss with age, are helpful as a general guide when counselling patients with Usher's syndrome as to the potential for visual loss with age. This type of information has important implications for vocational training.

The value of such data would be enhanced by the pooling of similar observations from several different investigators if a larger sampling within older, as well as younger, age groups could be obtained.

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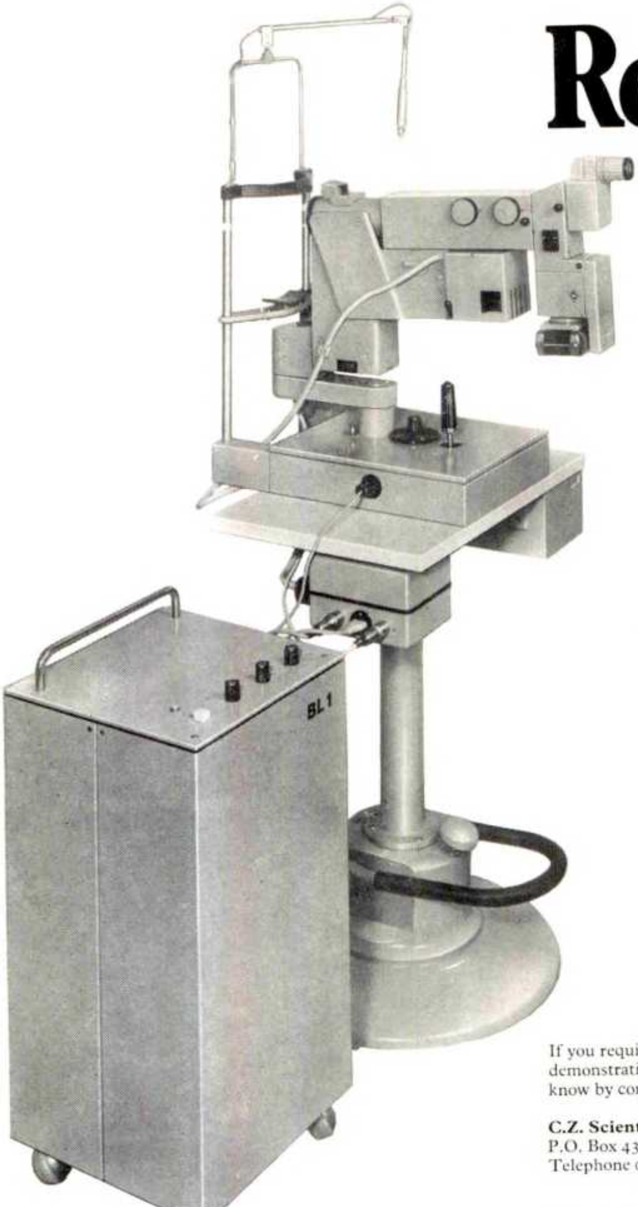

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Excessive permeability in diabetic maculopathy

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From the Hammersmith Hospital, Royal Postgraduate Medical School, and Moorfields Eye Hospital, London

SUMMARY Four cases of diabetic maculopathy with excessive permeability are described. Fluorescence angiography is distinctive, showing profuse early leakage from the entire capillary bed of the posterior pole. Careful studies have failed to reveal any cause for this excessive permeability response at the macula or any constantly associated medical abnormality. The prognosis for visual acuity is poor, and photocoagulation has only rarely been successful in maintaining or improving vision in these patients.

Diabetic maculopathy continues to be a major problem in diabetic patients of all ages. Visual acuity is often severely affected, and treatment by photocoagulation has not had the same highly favourable results as in the treatment of proliferative retinopathy with disc new vessels (DRS, 1976; British Multicentre Group, 1977). The natural history of diabetic maculopathy has never been clearly elucidated, probably because it embraces several subgroups which behave differently. In this communication we describe one particular rare subgroup. This unusual form of maculopathy is characterised by excessive permeability of all capillaries of the posterior pole. On examination, little or no abnormalities are seen apart from the oedema. On fluorescein angiogram there is early extensive leakage from the capillaries in the macular area.

Case reports

CASE 1

A 29-year-old nursing sister was referred to the Hammersmith Hospital in 1974 because of diabetic retinopathy. In the past she had episodes of iritis in both eyes (1970–72). She had noticed gradual deterioration in vision in her left eye in 1972 and more sudden, severe loss of vision especially in the right eye in 1973. She had been diabetic since the age of 13. Her treatment was a single daily dose of lente insulin, initially 100 units, reduced to 44 units in recent years, and she always had heavy glycosuria. Over the 6 months before coming to the Hammersmith Hospital she had noticed swelling of her ankles. It was only partially controlled by taking frusemide 80 mg daily.

On examination, her visual acuities (VA) were 6/18 on the right (R) and 6/24 on the left (L). She had no rubeosis, her intraocular pressure was normal, as were her anterior chambers. She had early cortical cataracts. The vitreous was normal; in particular no cells were seen. Fundus examination showed cystic macular oedema and early disc new vessels in both eyes (Fig. 1*a*). General examination showed that she was of ideal body weight; her blood pressure (BP) was 140/80 mmHg lying and standing. She had foot and ankle oedema, absent ankle reflexes, and reduced vibration sense.

Investigations showed normal blood urea, creatinine, cholesterol, triglycerides, haemoglobin (Hb), and white cell count (WBC). Serum proteins were normal, but albumin was at the lower limit of normal. Her blood sugar control was poor, and most blood sugars were over 15 mmol/l whatever time of day they were taken.

Florescein angiograms showed good initial capillary perfusion, with early profuse leakage from all the capillaries in the macular region, and disc leakage (Fig. 1*b* and *c*).

Medical course. General diabetic control was improved by changing her insulin dosage to soluble and isophane (NPH) 8 units each twice daily. Over the last 4 years her urine has been mostly free of sugar and blood sugar levels were mostly less than 9 mmol/l. Her ankle oedema persists but is improved on frusemide 120 mg/day and spironolactone 50 mg 3 times daily. In 1978 further blood tests investigating capillary endothelial damage by measuring factor VIII levels, platelet aggregation,

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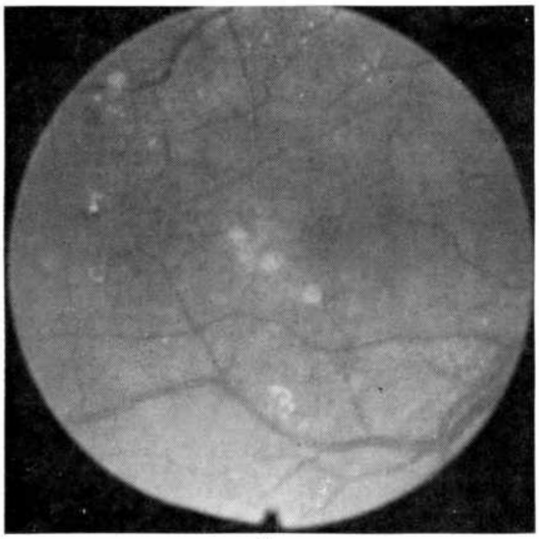

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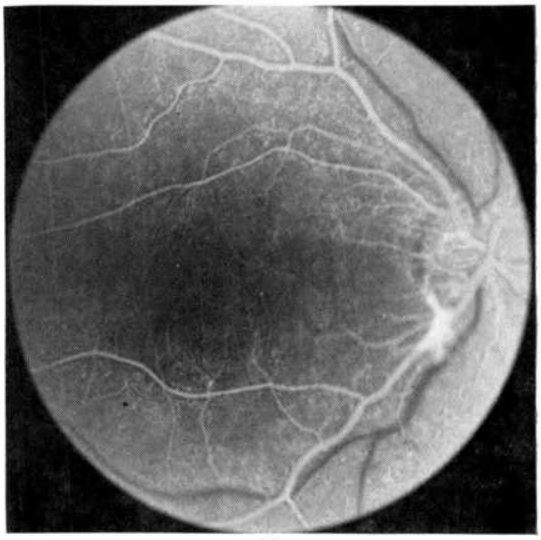

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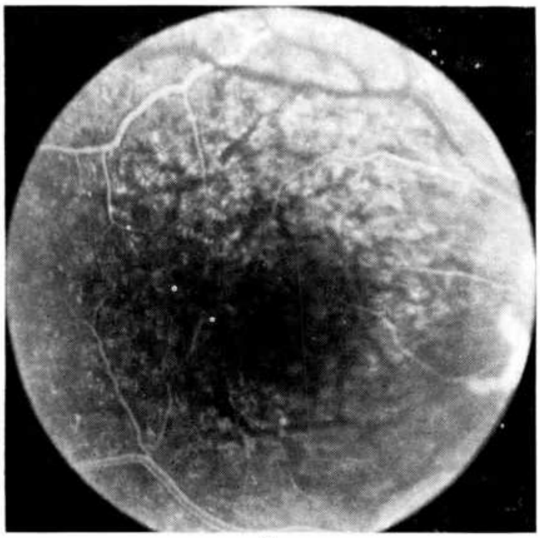


1c

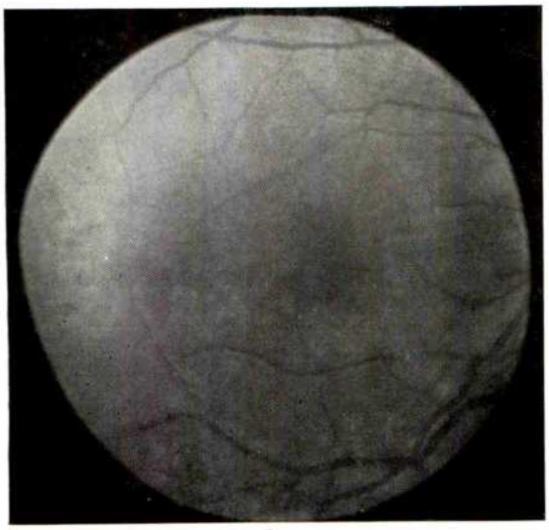
Fig. 1 (a) *From a colour photograph of R macular region from Case 1 when patient first seen. The perifoveal area looks featureless and there are only a few hard exudates and haemorrhages peripherally.* (b) *Fluorescein angiogram in capillary phase from Case 1 when first seen. Diffuse leakage.* (c) *Same as Fig. 1*b *but in late phase showing extensive leakage throughout posterior pole*

serum fibrinogen, and fibrin degradation products were normal. Blood urea, serum electrolytes, creatinine, and proteins remained normal, and no specific cause for the excessive capillary leakage was thus found.

Ocular course. In 1974, because of the severe retinopathy, she entered the paired eye photocoagulation study (British Multicentre Group, 1977). The right eye was drawn for treatment with the xenon arc (448 burns given as a pattern bombing). The left eye was untreated as a control. Over the 4 years' follow-up the vision in the right eye has remained static. Vision in the left eye has deteriorated to 6/60 (partly owing to increase in lens opacities). The macular oedema persisted, and fluorescein angiograms of the right eye remained the same (Fig. 2*a–c*). New vessels in both eyes have improved.

CASE 2

A 50-year-old parole officer was referred to the Hammersmith Hospital in February 1974 because of blurred vision. The ocular symptoms had been present since he began treatment for his diabetes 2 years previously. His vision had previously been excellent. At the age of 48 years he had presented to his local doctor with blurred vision, impotence for



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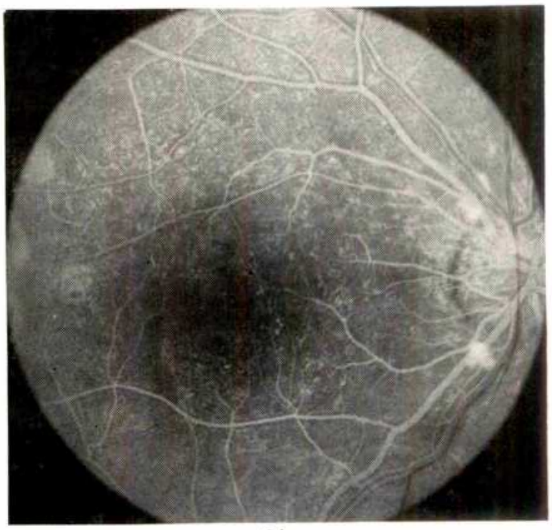

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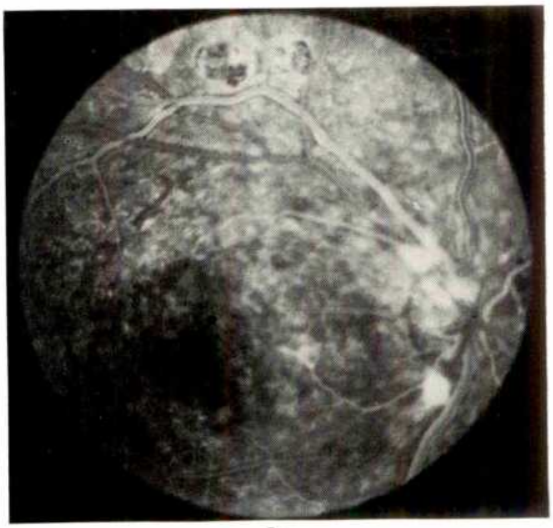

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Fig. 2 (a) *Same as Fig. 1a, but 4 years later. Photocoagulation scar seen lateral to macula. Note apparent normality of macular area.* (b) *Fluorescein angiogram of right macula of Case 1, 4 years after photocagulation. Extensive leakage in capillary phase still present.* (c) *Extensive leakage from all capillaries in late phase of fluorescein angiogram*

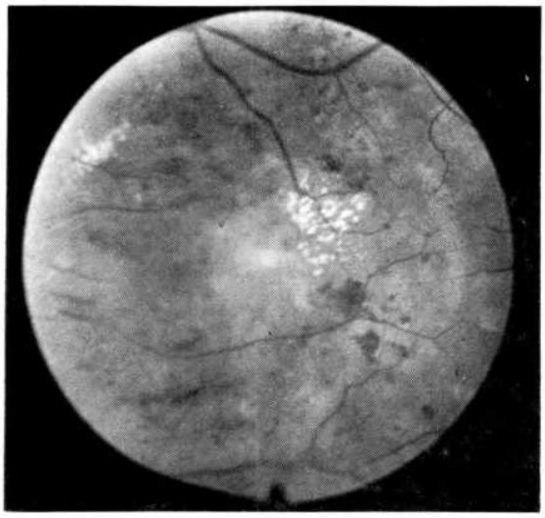
2 years, and increasing thirst, polyuria, and weight loss. The diagnosis of diabetes was made, and treatment with a 120-g carbohydrate diet, glibenclamide 12·5 mg, and long-acting phenformin 50 mg daily started. From that time blood sugars taken at the clinic were all well under 10 mmol/l.

On examination his visual acuities were R 6/6 and L 6/9. He had no rubeosis, normal intraocular pressures, and normal anterior chambers. Fundus examination showed bilateral cystic macular oedema (Fig. 3*a*). His BP was raised at 180/115 mmHg, and he had reduced vibration sense. Otherwise medical examination was normal, and in particular he had no ankle oedema, no signs of peripheral neuropathy, and was only 5% above ideal body weight.

Investigations showed normal blood urea, proteins, triglycerides, cholesterol, Hb, and WBC. Blood sugars were under 10 mmol/l. He had no proteinuria.

Fluorescein angiography showed symmetrical maculopathy with early good perifoveal perfusion, and early profuse leakage from all the capillaries at the posterior pole (Fig. 3*b–c*). There was also some peripheral capillary non-perfusion.

Medical course. Blood pressure was controlled with clonidine and beta blockers, but diabetic management has been maintained unchanged. He has kept in good health and maintained good control of his BP and diabetes. In 1978 further blood tests



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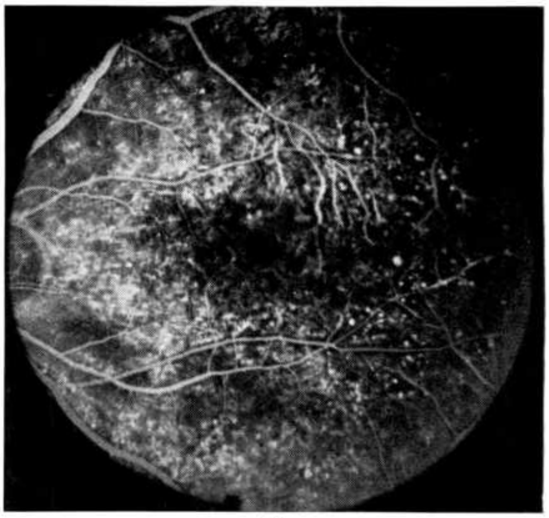

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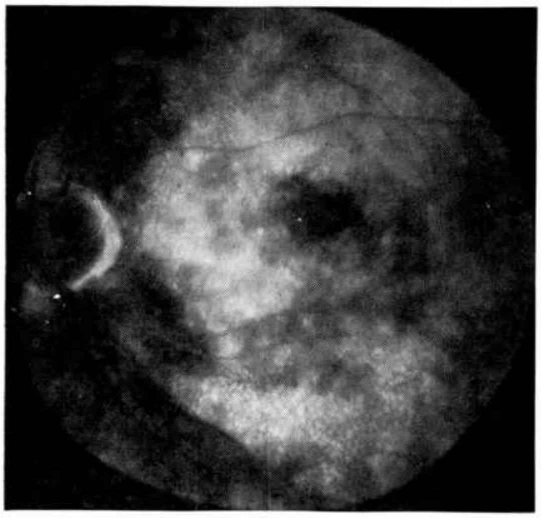


3c

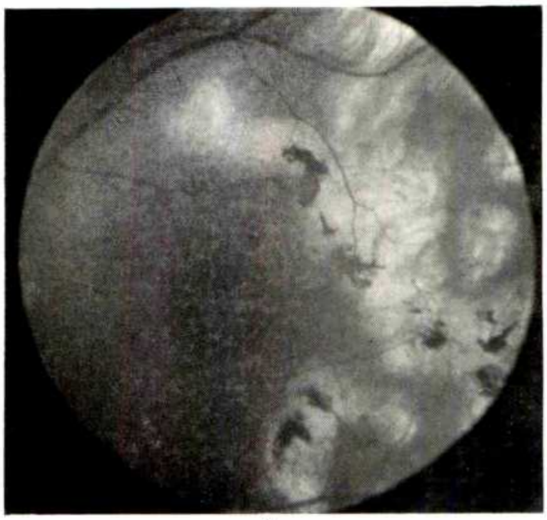
Fig. 3 (a) *Case 2 from colour photograph of left macular area showing haemorrhages and exudates in the macular region.* (b) *Fluorescein angiogram in capillary phase shows good perfusion and early leakage.* (c) *Fluorescein angiogram in late phase shows diffuse leakage throughout the macular area*

searching for evidence of generalised capillary endothelial damage showed factor VIII levels, platelet studies, fibrinogen, and fibrin degradation products to be in the normal range.

Ocular course. In 1974 he was entered in the paired eye photocoagulation trial (British Multicentre Group, 1975), and the left eye was drawn for xenon arc photocoagulation (335 burns as a pattern bombing). The right eye was untreated as a control. Over the 4 years' follow-up vision has decreased gradually to 6/60 in both eyes by 1978. Visual loss has been due to persistent gross leakage at the maculae leading to cystic macular oedema and finally bilateral macular holes (Fig. 4*a–c*).

CASE 3

A 42-year-old builder presented to Moorfields Eye Hospital in 1977 complaining of decreasing vision in both eyes. Diabetes had been diagnosed at 32 years of age when he presented to his local doctor with weight loss and polyuria. He was treated with 44 units lente insulin as a single daily dose. His control had always been poor, showing 2% glycosuria most of the time. Control was made difficult by his high daily alcohol intake (approximately 16 pints of beer and 3 double whiskies). On examination his visual acuity was 6/9 in both eyes. He had no rubeosis, normal intraocular pressures, and normal anterior chambers. Fundus examination showed



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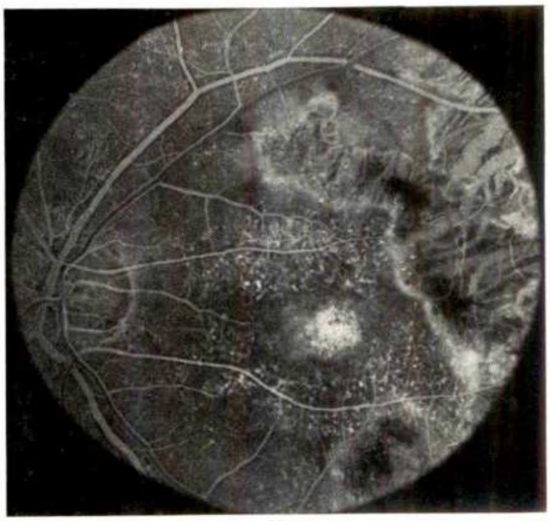

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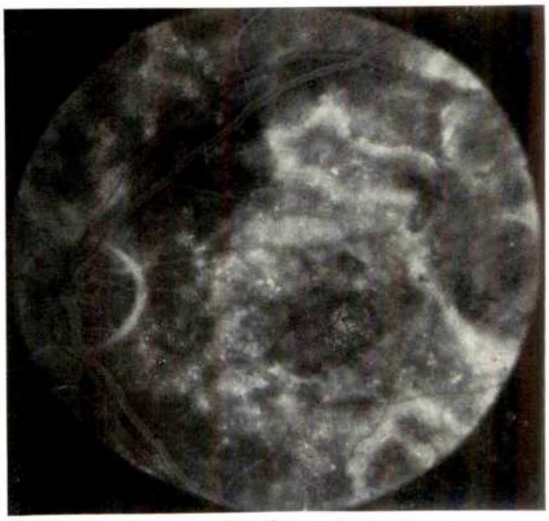


4c

Fig. 4 (a) *Case 2, 4 years after photocoagulation. Scars lateral to macula, cystic oedema, and macular hole.* (b) *Fluorescein angiogram in capillary phase shows that all remaining capillaries leak fluorescein. Note macular hole.* (c) *Fluorescein angiogram in late phase shows extensive leakage; unchanged from pretreatment angiogram*

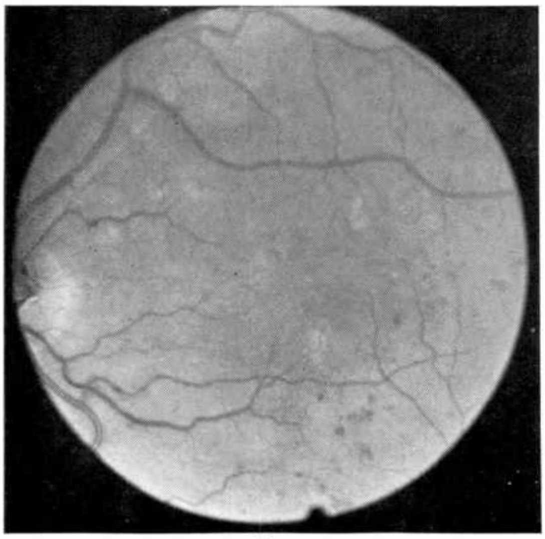
cystic macular oedema. General examination revealed a fit-looking man of ideal body weight, without diabetic complications apart from reduced vibration sense and absent ankle reflexes.

Investigations showed normal blood urea, triglycerides, cholesterol, Hb, and WBC. Factor VIII level, fibrinogen, fibrin degradation products, and platelet function tests were normal. His blood sugar levels were always above normal.

Fluorescein angiography showed good initial capillary perfusion and profuse early leakage from all the capillaries in the macular region.

Medical course. Over the 12 months to 1978 his diabetic control remained very poor but otherwise he was well. Because of his poor diabetic control he was admitted to the Hammersmith Hospital and treated for 2 weeks with continuous subcutaneous insulin infusion (Pickup *et al.*, 1978). On this regimen blood sugars were mostly below 10 mmol/l throughout the 24 hours. He was discharged on twice-daily soluble and isophane insulin and maintained improved control. However, at this time on his local doctor's advice he recommenced single daily insulin injection, with deterioration of his diabetic control.

Ocular course. His visual acuity had fallen to VAR 6/36 and VAL 6/60 despite argon laser treatment to both posterior poles—given as a focal and



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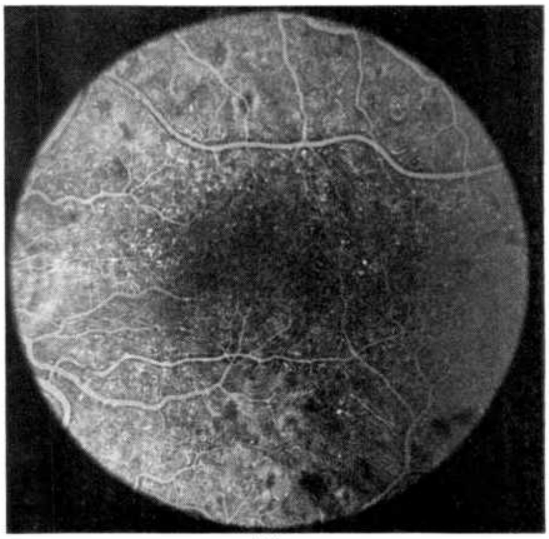

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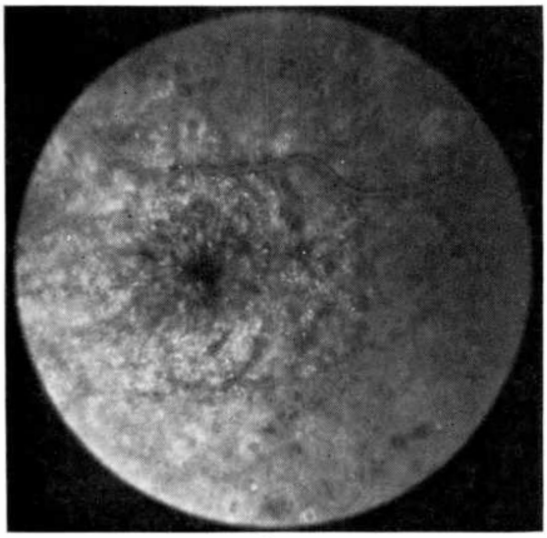

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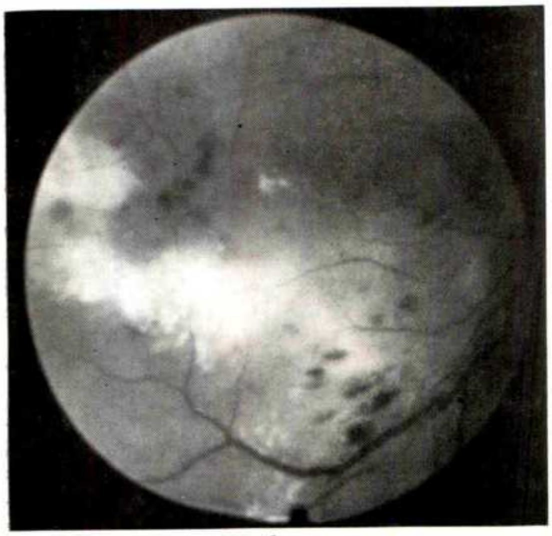
Fig. 5 (a) *Case 3 from a colour photograph of left macula after 400 argon laser burns and 2 weeks on continuous insulin infusion. Cystic macular oedema, haemorrhage, and laser scars visible.* (b) *Fluorescein angiogram in capillary phase showing dilated leaky vessels.* (c) *Fluorescein angiogram in late phase shows cystic macular oedema and leakage*

grid pattern, 87 burns on the right and 400 burns on the left prior to admission to hospital. While on continuous insulin infusion his vision improved to R 6/24 and L 6/18, though the fundus appearance and fluorescein angiogram remained the same (Fig. 5*a–c*). At his last visit, 2 months after discontinuing twice daily insulin, his visual acuity had decreased to R 6/60 and L counting fingers. The fluorescein angiogram was unchanged.

CASE 4

A 52-year-old clerical worker presented to the Hammersmith Hospital in 1974 after loss of vision in both eyes over the preceding 9 months. One year previously she had been diagnosed diabetic, after presenting to her local doctor with symptoms of thirst, weight loss, and frequency. At that time her vision was normal. The diabetes had been treated with 100-g carbohydrate diet, long-acting phenformin 50 mg twice daily, and chlorpropamide 500 mg daily.

On examination her visual acuities were VAR and VAL 4/60 each. She had no rubeosis, normal intraocular pressures, normal anterior chambers, and early cortical lens opacities. Fundus examination revealed cystic macular oedema. On general examin-



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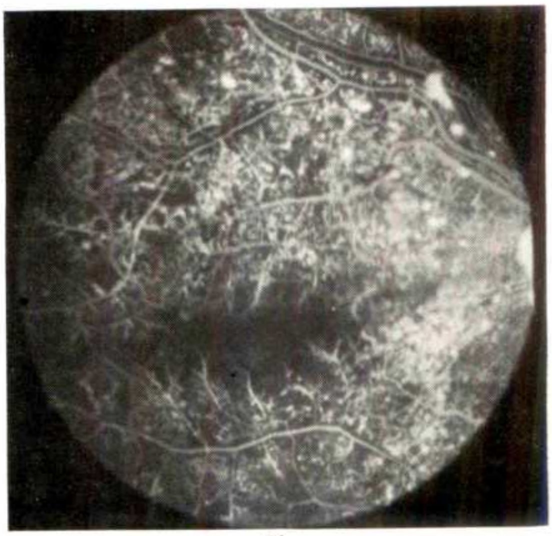

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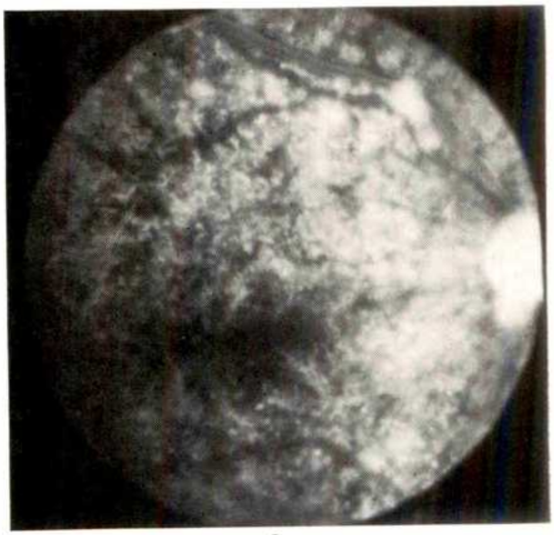

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Fig. 6 (a) *Case 4. Colour photograph of right macular region shows confluent hard exudates. There are also multiple haemorrhages.* (b) *Fluorescein angiogram in capillary phase showing marked dilatation of capillaries and leakage.* (c) *Extensive fluorescence of posterior pole in late phase of angiogram indicates widespread hyperpermeability. New vessels on disc seen at edge of picture*

ation she was of ideal weight with very few abnormal findings apart from slightly raised BP at 160/100, a raised resting pulse of 110, and absent ankle reflexes.

Investigations showed normal blood urea, proteins, cholesterol, triglycerides, Hb, and WBC. Her urine was always free of sugar and protein.

Fluorescein angiography showed extensive early leakage from all the capillaries at the posterior pole with areas of peripheral non-perfusion.

Medical course. Her general health remained good, but her blood urea had risen to 11·4 mmol/l, while her serum creatinine remained normal. During the last year her diabetic control had deteriorated and blood sugars are now 10 to 15 mmol/l. Further investigations in 1978 for signs of generalised capillary damage, factor VIII, prothrombin time, fibrinogen, fibrin degradation products, and platelet studies were all normal.

Ocular course. In 1974 she was entered in the paired eye photocoagulation study, and the left eye was drawn for xenon arc photocoagulation in a peripheral pattern bombing 250 burns. Both eyes deteriorated rapidly. The right, untreated eye developed disc new vessels and confluent hard exudates within 1 year (Fig. 6*a–c*), and thrombotic glaucoma proceeded to no light perception. The left eye lost further vision from retinal detachment to counting fingers at 1 metre.

Discussion

The patients presented here all had maculopathy of of a severe nature. All the capillaries at the posterior pole leaked fluorescein immediately the dye reached them.

It is not clear from our observations why these patients should have had such extensive leakage. There was no evidence of any inflammatory process in the eyes. Only 1 of the 4 patients (Case 1) had mild proteinuria and severe ankle oedema, indicating hyperpermeable capillaries in other parts of the body. Moreover, blood tests done to identify generalised endothelial cell damage—factor VIII related antigens, fibrinogen, fibrin degradation products—were normal. It is known that capillaries in skeletal muscle of long-term diabetics have increased permeability (Trap-Jensen and Lassen, 1968), but the cause of this is not known, and it is not necessarily associated with extensive retinal capillary leakage leading to maculopathy in most diabetics. Schatz and Patz (1976) reported a group of diabetics with this type of maculopathy and noted that these patients were all young. While 2 of our patients were less than 45, 2 were 50 or more, indicating that youth is not necessarily a feature of the condition. A similar type of maculopathy has been observed in some young, pregnant diabetics and women on oral contraceptive pills. In contrast to the 4 patients reported here, in these women the cystic macular oedema has improved on treatment with diuretics, stopping the pill, or completing the pregnancy.

Renal function was remarkably normal in our present patients when they presented with visual loss. The effect of blood pressure on maculopathy has not been clearly established, but it appears that raised BP accelerates the progression of retinopathy in general (Harrold, 1971; Kohner, unpublished observation). Of the patients reported here only 1 had high BP and 1 mildly raised BP. Treatment of the BP did not alter the course of the retinopathy, and vision continued to deteriorate rapidly, irrespective of blood pressure levels. The role of diabetic control has not been clearly established in the development and treatment of this condition. The 2 insulin-dependent diabetics may have been favourably influenced by improvement of their control. The only eye which retained 6/18 vision belongs to one of the patients whose diabetes became well controlled with most blood sugars under 10 mmol/l. It is tempting to implicate poor diabetic control in the other young person as a cause of the severe loss of vision, especially as hospitalisation with near normal blood sugar levels during continuous insulin infusion improved his vision significantly. However, macular oedema may be variable, particularly when, as in this case, the patient's alcohol intake is drastically reduced. It remains no more than a clinical impression that it is worth while to optimise control in insulin dependent (type I) diabetics.

In the type II diabetics (Cases 2 and 4) blood sugar control was satisfactory when the severe maculopathy developed. The patient (Case 4) who was on maximum doses of oral hypoglycaemic agents probably should have been on insulin. Her poor vision detered us from changing her on to this treatment. Conclusions are difficult to make, but it is possible good control has very little beneficial effect on the retinopathy of type II diabetics. This impression is in agreement with the findings of the study by the UGDP (1977). Furthermore, it is possible that once a certain severe degree of retinopathy is present the lesions, especially non-perfused areas, are irreversible. In this as in other maculopathies there was a progressive occlusion of small vessels in the retinal periphery. In the first 2 patients it was observed at presentation. In Patient 4 it occurred during the period of follow-up, and in Patient 3 after completion of the report. Capillary non-perfusion occurs in all forms of diabetic retinopathy and is not thought to be relevant to the excessive permeability seen in these patients. Photocoagulation is of some benefit in most forms of maculopathy (Patz *et al.*, 1973; British Multicentre Group, 1975). In our group it seemed to have very little effect. This is in agreement with the findings of Schatz and Patz (1976), whose patients with severe macular oedema also did not respond to extensive treatment. In conclusion, in type I diabetics with this rare condition good physiological diabetic control should be aimed at in the first instance, photocoagulation should be tried early, but it is important to maintain a guarded visual prognosis.

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Macular pigment deposits in rhegmatogenous retinal detachment

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SUMMARY This is a study of 20 cases of macular pigment migration after operation for retinal detachment. The frequency of pigment deposits on the macula among the total number of operated detachments was 6·4%. The evolution of pigment migration depended on the form and type of the deposits. In some cases the pigment diminished or disappeared. In 6 of the 20 eyes with pigment migration puckering of the macula occurred 4 months or more after surgery. The improvement in visual acuity 6 months and more after operation was relatively less in the group with pigment deposits than in the group without pigment. In the former group static perimetry showed defects corresponding to the pigment migration.

Pigment migration or dispersal or fallout maybe a complication of rhegmatogenous retinal detachment or of retinal detachment surgery with cryoapplication. First described by Bietti (1934a, b), it is attributed to the release of pigment from the pigment epithelium in an area previously subjected to freezing. The pigment thus released is conveyed by the ocular fluids and deposited in various parts of the eye fundus. The pigment travels either transvitreally or by way of the subretinal fluid (Sudarsky and Yannuzzi, 1970; Hamilton and Taylor, 1972).

Various authors, such as Lincoff (1967), Abraham and Shea (1969), Sudarsky and Yannuzzi (1970), Chignell *et al.* (1973), Hilton (1974), and Theodossiadis *et al.* (1975b), have previously discussed the general aspects of pigment dispersal and with its causes, without, however, confining themselves exclusively to the migration of pigment to the macula and its consequences. The present study therefore aims at describing the incidence of pigment fallout in the macula, its evolution, and the effects of pigment deposits on the function of the macula.

Material and methods

Our investigation is based on 326 cases of rhegmatogenous retinal detachment operated on between January 1974 and January 1976. During this period a total of 402 rhegmatogenous retinal detachments were surgically treated. Anatomical restoration was achieved in 357 of these cases after one or more surgical operations. Of these 357 cases our investigation takes into account 326, the remaining 31 cases having been excluded as they could not be adequately studied.

The operation in all cases was in accordance with the Custodis-Lincoff procedure, which entails the placing of an episcleral Silastic sponge in conjunction with cryopexy. Drainage was employed in 152 of these 326 cases. In all instances the cryoprobe was applied under ophthalmoscopic control.

Of the total number of 326 cases 72 presented pigment migration into one or more retinal areas; 21 out of the 72 cases showed pigment deposits at least in the central part of the retina, that is, in the macula or the fovea or the foveola. It should be stressed that the group of patients with pigment migration in the macula includes only eyes with manifest pigment deposits. Cases with sparse pigment spots were not taken into consideration.

Of the 21 cases showing pigment deposits in the macula only 20 (group *A*) were followed up and examined, 1 case being eliminated because of macular puckering prior to the operation for retinal detachment. None of the 20 patients with macular pigment migration had been given a saline or air injection into the vitreous cavity during surgery. Of the 20 cases 2 showed pigment deposits confined solely to the fovea and foveola, whereas in the remaining 18 cases the deposits involved in addition to the fovea and foveola one or more retinal areas.

Depending on its form, pigment migration was classified into the spotty, patchy, striated, and mixed types. The spotty type included pigment accumula-

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Table 1 *Comparison of groups* A *and* B *regarding sex, aphakia, location of tears, number of cryoapplications, manner of Silastic sponge fixation, release or nonrelease of subretinal fluid, and postoperative uveitis*

Group A *(with macular pigment migration)*

Case no.	*Sex*	*Aphakia*	*Location of tears*	*No. of cryoapplication*	*Fixation of Silastic sponge*	*Release of subretinal fluid*	*Postoperative uveitis*
1	M*	+	SN†	21	E–R‡	+	–
2	F	+	SN–IN	27	E	–	–
3	M	+	ST	14	E	+	+
4	F	–	ST	7	P	+	+
5	M	+	ST	5	E	+	+
6	F	+	ST–IN	10	E	+	–
7	M	–	ST–SN	7	P–R	+	–
8	M	+	ST–IN	7	E	–	–
9	M	–	ST–IT	25	P	+	+
10	M	–	SN–IT	17	P	–	+
11	F	–	ST	22	P	–	–
12	M	–	ST	8	R	–	+
13	F	–	ST	12	P	–	+
14	M	+	ST	9	E	+	+
15	M	–	ST	11	P	+	+
16	M	+	SN–IT	6	E	–	+
17	F	–	ST	5	P	–	+
18	M	–	ST–IT	21	P	–	+
19	M	+	SN	13	E	+	–
20	F	–	ST	15	P–R	–	+

Group B *(without pigment migration)*

Case no.	*Sex*	*Aphakia*	*Location of tears*	*No. of cryoapplications*	*Fixation of Silastic sponge*	*Release of subretinal fluid*	*Postoperative uveitis*
1	F	–	IN	5	P	+	–
2	M	–	IT	8	E	–	–
3	F	+	ST–SN	11	E	+	–
4	M	–	ST	15	P	–	–
5	M	+	SN–IT	16	E	–	+
6	M	+	ST	10	E	+	–
7	F	–	ST	10	R–P	+	–
8	M	–	IT	6	E	+	–
9	F	–	IT–IN	22	P	+	–
10	M	+	SN	7	E	+	–
11	F	–	IT	20	P	–	–
12	M	–	ST	6	P	–	–
13	F	–	SN	21	P	+	–
14	F	–	ST	12	E	+	–
15	M	–	ST	14	P	–	–
16	M	–	SN–IN	14	E–R	+	–
17	M	–	SN	10	P–R	–	–
18	M	–	ST	15	P	+	–
19	F	–	SN	11	P	+	–
20	M	+	ST	13	P	–	–

* M = male, F = female. † ST = superior temporal, SN = superior nasal, IT = inferior temporal, IN = inferior nasal. ‡ E = encircling, R = radial, P = parallel to the limbus

tions in the fovea and foveola. Each accumulation comprised at least five or more spots of pinhead size. In accordance with the location of the pigment deposits these were divided into epiretinal and subretinal types.

To study the effects of the pigment deposits on the function of the macula we also examined an equal number of cases operated on for rhegmatogenous retinal detachment in accordance with the same method and by the same surgeons but lacking pigment deposits. The patients selected (group *B*) corresponded approximately to those with pigment migration in the macula (group *A*) in respect of age, refraction, extent of the detachment, macular involvement, and preoperative visual acuity. The cases in the control group, like those of group *A*, showed no preoperative degeneration or other alterations of the macula.

Table 1 sets out the sex, the presence or absence of aphakia, the location of the tears, the number of cryoapplications, the manner of placement of the Silastic sponge, the release or nonrelease of subretinal fluid, and postoperative uveitis in the patients of both groups. Temperature and duration of the cryoapplication were about the same in both groups. The temperature ranged from −45 to −60°C and the duration of the cryoapplication from 3 to 8 seconds, the average being 6·5 seconds.

During the follow-up of the cases of both groups at regular intervals visual acuity was examined, colour perception ascertained by means of the 100 hue test, photographs were taken and fluorescein angiography was carried out. Moreover, the patients were subjected to an examination with direct and indirect ophthalmoscopy, the Goldmann three-contact-lens, as well as to ERG and both kinetic and static perimetry. The duration of the follow-up period amounted to at least 24 months.

Results

FREQUENCY OF MACULAR PIGMENT DEPOSITS

The relative frequency of pigment migration and deposits in the macula amounted to 6·4% of the total number of retinal detachments. More specifically, of the 20 cases 8 concerned the foveola and 10 the fovea, while the remaining 2 cases were of the mixed type.

Analysis of the factors listed in Table 1 showed that some of them influenced pigment migration, while others were entirely irrelevant. Among the factors which exerted no influence on pigment migration were sex, aphakia, the manner of Silastic sponge fixation, and the release or nonrelease of the subretinal fluid. Among the factors that certainly operated should be reckoned postoperative uveitis and retinal tears located at the upper temporal quadrant and especially at the superior quadrants ($P<0·025$), while the number of cryoapplications should be taken into account in relation to the degree of temperature, the duration of each application and the degree of pressure exerted with the probe on the eyeball (Brihaye and Oosterhuis, 1972).

Details as to the form of pigment deposits, the elevation or absence of elevation of the macula, and the presence of macular puckering in conjunction with the time of its development after surgery for detachment are summarised in Table 2. Finally, Table 3 sets out the time of onset of pigment migration in relation to the time of surgery for the retinal detachment.

The analysis shows that preoperative pigment migration was observed mainly in aphakic eyes, in which the detachment appeared as long as 4 months after the operation for cataract, as well as in cases with highly elevated retina, the eyes of which were patched for 24 to 48 hours prior to the surgical

Table 2 *Type and location of pigment deposits in relation to macular elevation and puckering*

Case no.	*Pigment type*	*Location of deposits*	*Macular detachment*	*Macular puckering*
1	Sp.*	Epir.	−	+ 4 m†
2	Sp.	Epir.	+	+ 5 m
3	Sp.	Subr.	+	−
4	Sp.–pat.	Subr.	+	+ 6 m
5	Pat.	Subr.	+	−
6	Pat.	Subr.	+	−
7	Sp.	Subr.	+	−
8	Sp.	Subr.	+	−
9	Pat.	Subr.	+	−
10	Pat.	Subr.	+	−
11	Sp.–pat.	Epir.–subr.	+	−
12	Sp.–str.	Epir.	−	+ 5 m
13	Sp.–str.	Epir.	−	−
14	Pat.	Subr.	−	−
15	Sp.	Epir.	+	−
16	Sp.–pat.	Subr.	+	−
17	Sp.	Epir.	−	−
18	Sp.	Epir.	−	−
19	Sp.	Epir.	−	+ 4 m
20	Sp.–pat.	Epir.	+	+ 4 m

* Sp. = spotty, pat. = patchy, str. = striated, epir. = epiretinal, subr. = subretinal. † m = months after retinal detachment surgery

Table 3 *Time of onset of pigment migration in relation to the time of operation*

Time	*Preoperatively*	*During or immediately after operation*	*Postoperatively (up to 10 days)*
Cases	4	13	3

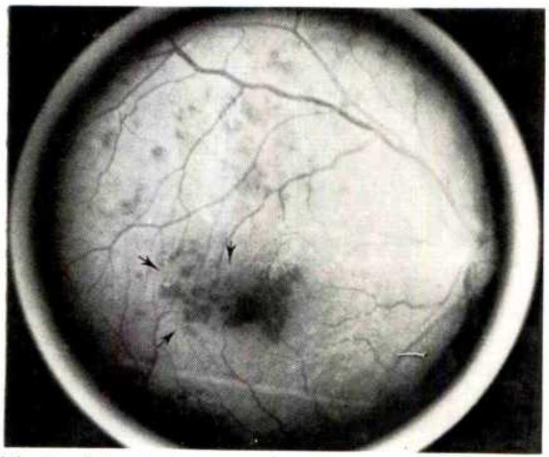

Fig. 1 *Subretinal pigment deposits in the central area 4 months after successful retinal detachment operation. Visual acuity 0·4*

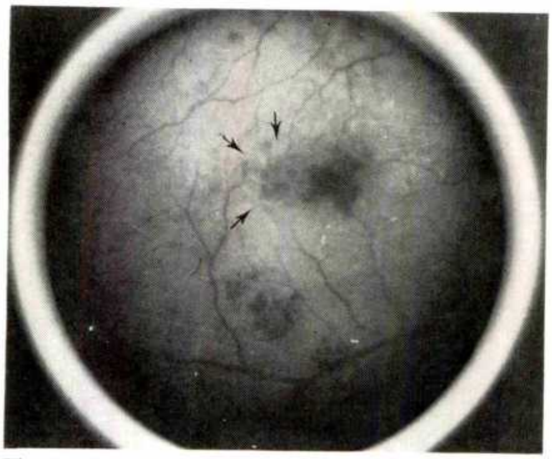

Fig. 2 *Same patient as in Fig. 1, 17 months after operation. Although pigment deposits in the foveola and fovea persist, there is a relative diminution of their concentration and extent. It is also to be noted that certain patches on the macula have vanished (see arrows). Visual acuity remains unchanged (0·4)*

intervention. In all instances of preoperative pigment migration the location of the pigment was epiretinal. All 3 cases which presented macular pigment migration after surgery for retinal detachment also showed postoperative uveitis.

With respect to location, epiretinal pigment deposits were encountered: (*a*) in cases with preoperative pigment migration, and (*b*) in retinal detachments without any elevation of the macula.

In the cases of subretinal location of the pigment deposits there invariably pre-existed a preoperative macular elevation, while the retinal detachment was pre-eminently superior or superor-temporal. Subretinal pigment deposits were observed during surgery or immediately afterwards.

EVOLUTION OF THE PIGMENT DEPOSITS

In the cases in which the pigment deposits were subretinal alterations of the pigment were observed, although they were smaller in extent and number than those in the group with epiretinal deposits (Figs. 1 and 2). The latter presented changes consisting in the displacement of the pigment from the foveola to the fovea or even farther away and in the diminution of the size of the pigment spots or patches. These were observed in 4 of the 10 cases with epiretinal pigment deposits (Figs. 3 and 4).

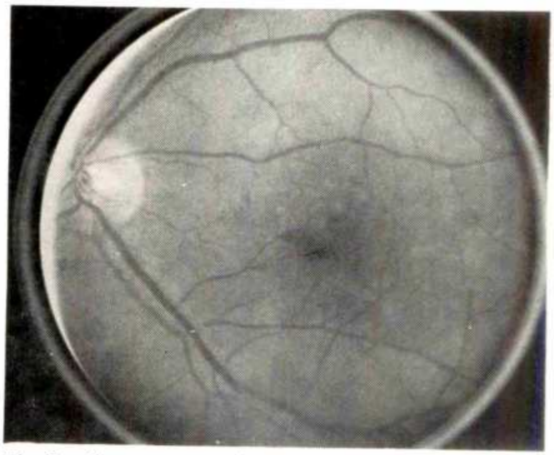

Fig. 3 *Pigment accumulations of epiretinal type on the foveola and fovea 3 months after operation. Visual acuity 0·9*

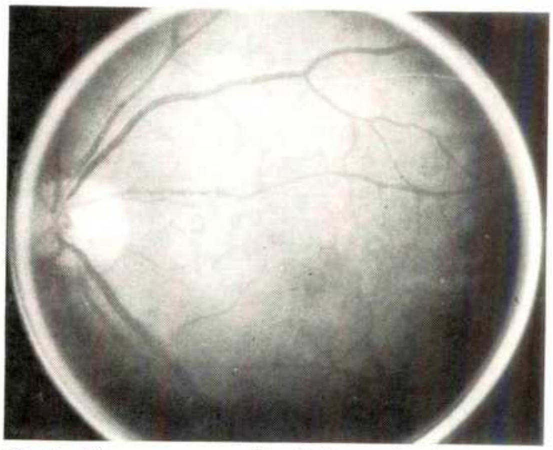

Fig. 4 *The same case as Fig. 3, 27 months after operation. Note that the pigment deposits have almost dispersed*

The changes in the pigment migration were noted after the first 12 months following the operation.

Six out of the 20 cases with pigment deposits in the foveola or fovea developed postoperative puckering of the macula. In all these 6 eyes pigment deposits preceded the macular puckering, which occurred 4 months or more after the operation. The appearance of macular puckering in the group with pigment deposits is statistically significant, since it arose in 6 out of 20 cases, whereas in the comparison group none of the 20 cases was subject to it ($P<0{\cdot}01$). Macular puckering was more frequent (5 out of the 6 eyes) in cases of epiretinal deposits of the spotted type.

Details concerning the relation between macular puckering and the type and location of the pigment and the time of onset after the surgery for the detachment are set out in Table 2. It should also be noted that in the group with pigment migration there was 1 case with a partial macular hole and 1 with cystoid macular degeneration. The partial macular hole appeared after the fourth month and the cystoid degeneration 1 year after the operation (Fig. 5).

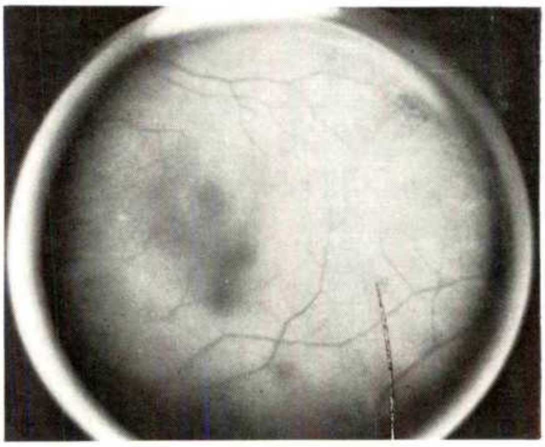

Fig. 5 *Pseudohole of the macula which developed 4 months after operation in a 53-year-old patient. The pigment covers two-thirds of the macular periphery but is more evident in the inferior temporal area*

EFFECTS ON FUNCTIONAL CONDITION OF THE MACULA

In the 14 cases with macular pigment migration in which no puckering of the macula was observed the greatest improvement of visual acuity was achieved within the same time as in the group without pigment migration, mainly in the first 6 months after operation. Average visual acuity, however, was better in the group without pigment migration, given the fact that 12 out of the 14 eyes in this group had better visual acuity taken singly and all 14 in the aggregate at 3, 6, and 24 months after operation (Tables 4 and 5, Fig. 6). It should be pointed out that to facilitate comparison the 6 cases with macular puckering of the group with macular

Table 4 *Comparison between visual acuity of the 2 groups up to the 6th postoperative month**

Case no.	*Visual acuity*					
	Group with macular pigment migration			*Group without pigment migration*		
	Preoperation	*3 months after operation*	*6 months after operation*	*Preoperation*	*3 months after operation*	*6 months after operation*
1	0·05	0·3	0·3–0·4	HM	0·5	0·7
2	0·05	0·4	0·5	HM	0·9	0·9
3	HM	0·3	0·4	HM	0·4	0·6–0·7
4	CF	0·3	0·3	CF	0·3	0·4
5	0·2	0·1	0·1	0·2	0·6	0·7–0·8
6	0·3	0·4–0·5	0·5	HM	0·3	0·6
7	HM	0·2	0·2–0·3	0·05	0·2–0·3	0·3
8	CF	0·2	0·3	CF	0·3	0·6
9	0·8–0·9	0·9	0·9	0·3	0·6–0·7	0·8
10	HM	0·7	0·7–0·8	CF	0·4	0·5–0·6
11	HM	0·2–0·3	0·3	HM	0·6	0·7
12	0·3	0·4	0·5	0·3–0·4	0·3	0·4
13	0·9	0·8	0·8–0·9	0·9	0·9	0·9
14	0·9	0·9	0·9	0·9	0·9	0·9

* Cases of macular puckering of group *A* have been omitted, as well as the 6 corresponding cases without puckering from group *B*. HM = hand movements, CF = counting fingers

Table 5 *Statistical analysis of improvement of visual acuity in groups* A *and* B *in the 3rd, 6th, and 24th postoperative month*

Group A. *Initial visual acuity/3, 6, 24 postoperative month*

Months after operation	t *value*	*Probability*	*Significance*
3	1·56	P>0·1	No
6	2·00	P<0·1	Yes
24	2·29	P<0·05	Yes

Group B. *Initial visual acuity/3, 6, 24 postoperative month*

Months after operation	t *value*	*Probability*	*Significance*
3	3·03	P<0·01	Yes
6	4·57	P<0·001	Yes
24	5·27	P<0·001	Yes

Progress of group A*/progress of group* B

Months after operation	t *value*	*Probability*	*Significance*
3	1·62<1·7	P>0·1	Not or hardly significant
6	2·34	P<0·05	Yes
24	2·45	P<0·05	Yes

pigment migration were excluded, as also were the 6 corresponding cases without macular puckering of the comparison group.

The 100 hue test did not reveal any differences between the 2 groups in respect of colour perception, nor were any differences observed in the ERG between the 2 groups. In contrast the group with pigment migration showed defects by static perimetry (Fig. 7).

For the latter examination eyes were selected from among both groups having a visual acuity of at least 0·7 and over and subjected to kinetic and static perimetry after the sixth postoperative month and later. During static perimetry it was observed that the pigment deposits, irrespective of type and form, gave rise to corresponding defects in the visual field, whereas the results of kinetic and static perimetry in group *B* showed no such defects.

Discussion

It has been established that after a rhegmatogenous retinal detachment, and in particular after its surgical treatment, pigment migrates and is deposited anywhere in the fundus. The location of the pigment after the onset of the detachment and before the surgical operation has been clinically observed by Theodossiadis *et al.* (1975a, b) as well as experimentally established by Laqua and Machemer (1975). Preoperative pigment migration was more frequent in aphakic eyes which had recently undergone surgery for cataract.

Generally speaking, macular pigment migration was relatively more frequent in cases with upper temporal location of the tears ($P<0·1$), while generally with a superior location of the tears migration to the macular area was even more frequent and statistically significant ($P<0·025$). In such cases and under the given conditions it would perhaps be advisable to position the patient's head with an upper nasal or temporal turn, depending on the location of the tears, during the first and perhaps second postoperative day.

The further evolution of the pigment depended on the type of the pigment deposit. Thus, in the epiretinal type 4 cases showed a marked diminution or displacement of the pigment away from the macula, occurring after the first 12 months after operation and resulting in 2 cases in an improvement of visual acuity.

So far there is no satisfactory explanation of the effects on the macula's functional condition of the

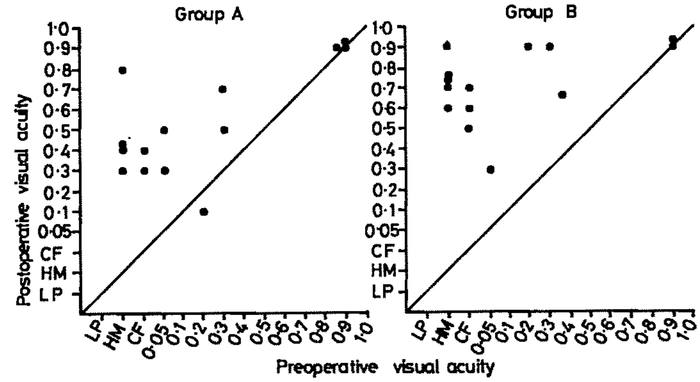

Fig. 6 *Comparative study of visual acuity in groups* A *and* B *preoperatively and 2 years after operation*

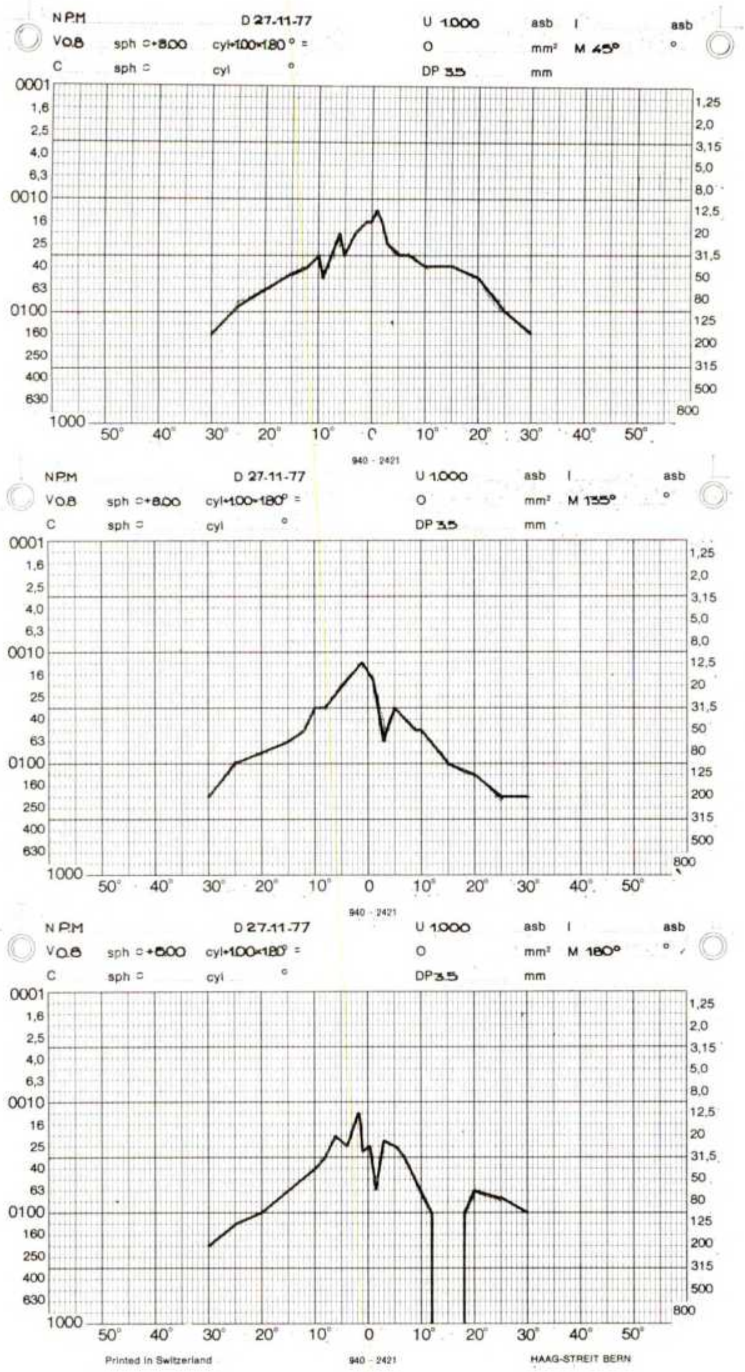

Fig. 7 *Static perimetry in a 60-year-old patient with epiretinal pigment migration. Visual acuity 0·8. Note defects corresponding to the pigment deposits*

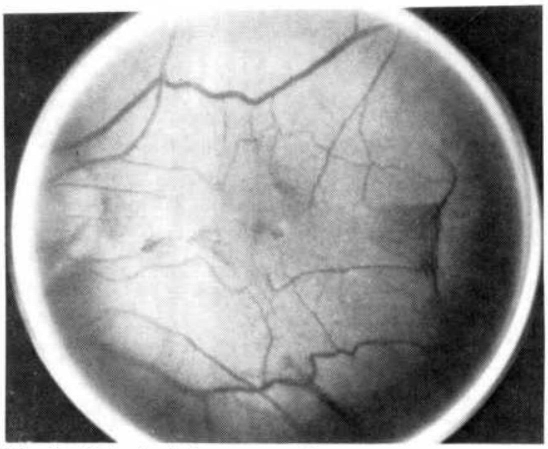

Fig. 8 *Epiretinal pigment membrane at the posterior pole of the eyeball in a patient aged 70. The membrane resulted in the formation of macular puckering. The pigment in this case was of the mixed type*

migration and deposition of pigment in this area, and the views that have been put forward are in many respects controversial.

Thus, Sudarsky and Yannuzzi (1970) stated that pigment in the fovea is probably the most serious complication in cryosurgery, but that statistical evidence was still required to prove this. Norton (1969) likewise drew attention to the risks of excessive freezing and indicated the need for further investigation into the effect of pigment on the visual function. Abraham and Shea (1969) stressed that the effect of pigment accumulation on vision still awaits clarification and that pigment is likely to induce a relative scotoma corresponding to the site of its accumulation. Hilton (1974) claimed on the contrary that visual acuity and the function of the macula in general are not affected by macular pigment migration and deposits.

Our own results argue in favour of the view that the function of the macula is indeed impaired by the migration and deposition of pigment on it. This fact emerges from the comparison of the visual acuity of our 2 groups of patients with and without deposits of macular pigment. The comparison clearly shows that the cases of the group without pigment migration had better visual acuity 3, 6, and 24 months after operation (Tables 4 and 5, Fig. 6). The difference in visual acuity is statistically significant, especially after the first 6 months ($P<0\cdot05$).

It should be noted that no difference was established in respect of visual acuity between the groups with epiretinal and with subretinal pigment migration.

Furthermore, static perimetry in the cases of the group with pigment deposits and visual acuity equal to or above 0·7 has shown that there is a relative defect corresponding to the pigment accumulation, whereas in the control group with the same visual acuity and without pigment deposits static perimetry showed no defect.

Pigment deposits in the macula, especially of the epiretinal type, seem to lead to macular puckering in a greater proportion of instances than when there are no pigment deposits (Fig. 8). This observation is statistically significant ($P<0\cdot01$), as appears from the analysis of our cases (Table 2). Puckering consequent upon pigment migration was also noted by Robertson and Buettner (1977) and by Clarkson *et al.* (1977). An explanation of this phenomenon has been attempted by Laqua and Machemer (1975), Machemer and Laqua (1975), and Johnson and Foulds (1977), who on the strength of their experimental investigations have postulated that migrating cells from the pigment epithelium may act as macrophages, and that these cells conjointly with glial cells are partly responsible for preretinal and retroretinal membrane formation. Such membrane formation, however, does not invariably ensue and cannot always be predetermined. It must be noted that in our cases the appearance of puckering consequent upon the deposition of pigment occurred relatively later, that is, 4 months and later after the operation, than the usual occurrence of puckering without the presence of pigment deposits.

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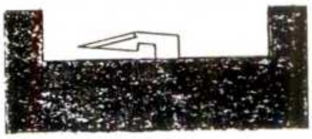

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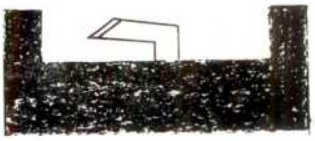

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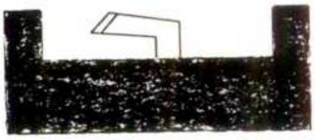

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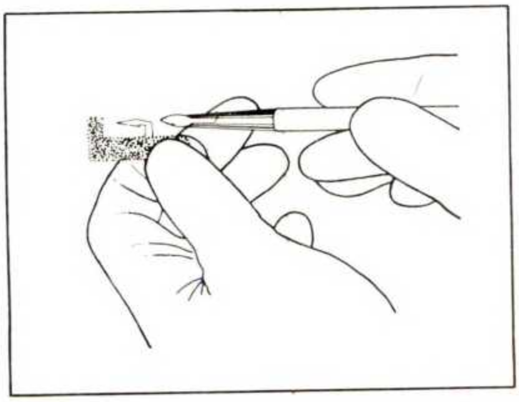

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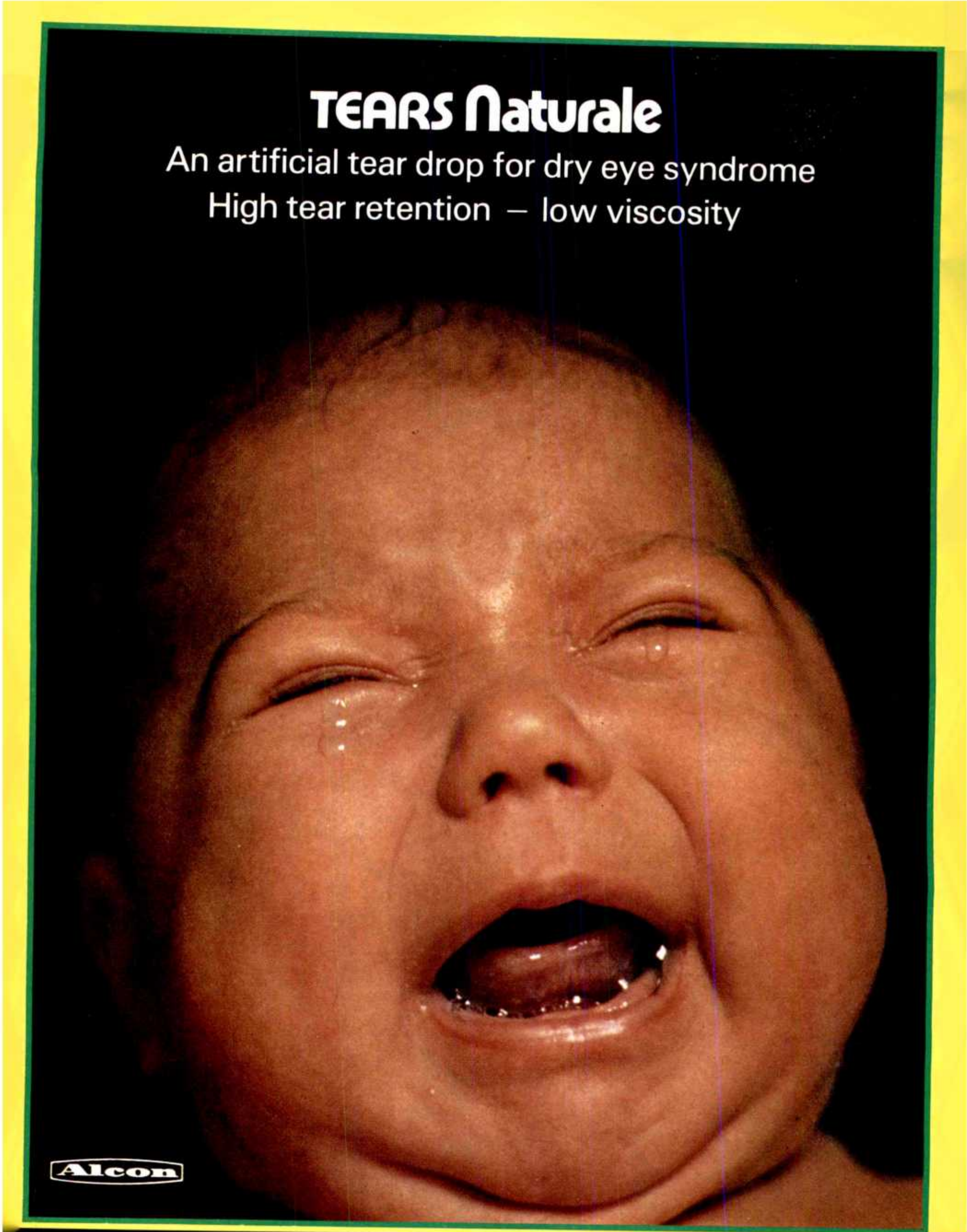
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British Journal of Ophthalmology, 1979 **63**, 507-510

The fishmouth phenomenon in retinal detachment: old concepts revisited

COLIN H. BIRCHALL

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SUMMARY The 'fishmouth phenomenon' seen in some previously treated retinal detachments is associated with large horseshoe tears and scleral buckling techniques. A method of treating patients with this complication is described in which scleral buckling with implant or explant is *not* used. The technique utilises intravitreal air tamponade with cryopexy and gives good results. The incidence of patients developing the fishmouth phenomenon as a complication of primary simple retinal detachment surgery is much lower when an intravitreal air technique is used than the expected incidence following a primary scleral buckling operation.

The objective of this paper is to describe the management of difficult large posterior horseshoe-tear retinal detachments which develop the aptly named 'fishmouth phenomenon', in which a second surgical procedure is required following a failure of scleral buckling with scleral silicone implant or explant and/or encircling silicone tape.

The prognosis for reattachment of the retina in routine retinal detachment surgery for primary rhegmatogenous detachments, by different surgical techniques, is now well documented. The results from different series indicate reattachment in 90 to 95% of patients (Kreiger *et al.*, 1971; Chignell, 1977; and Curtin, 1976). The reduced chance of a successful first surgical procedure in more complicated detachments, for example, detachments due to macular holes (Leaver and Cleary, 1975) and in secondary detachments is also recognised.

Results of operations for detachment where the primary process of detachment involves retinal lesions with large posterior tears suggest that the larger the tear the worse the prognosis (Lincoff *et al.*, 1977). At the worst a giant tear may extend through almost 360° and is virtually unmanageable with present surgical techniques. Difficulties are encountered in routine scleral buckling procedures with large horseshoe tears when the buckle causes the operculum of the tear to elevate as the rolled edges of the tear come closer together. This compromising effect is greater with circumferential buckles than with radial buckles. If further tightening of an encircling tape is attempted at this time, it serves only to elevate the operculum further, hence the fishmouth phenomenon (Figs. 1 and 2).

Recent descriptions of the geometrical considerations of the sequelae of scleral buckling (Pruett, 1977) correctly and succinctly conclude that 3 factors contribute to the pathogenesis of the fishmouth phenomenon. These factors are: (1) the relative length of the buckle (relative to the circle of the eye that is being indented); (2) the height of the buckle, which in turn is related to the tension of the encircling tape and the depth of cross-section of the implant or explant; and (3) the shape of the edge of the implant or explant used.

Thus the fishmouth formation is associated with large horseshoe tears and scleral buckling techniques, but it has not been observed in the past 4 years by this author when such tears have been treated surgically without scleral implanting or explanting. It seems logical, therefore, to treat patients with large horseshoe tears, if they require reoperation, without any scleral implant or explant, and results from this series indicate that this can be satisfactorily performed.

Method

All the patients had been previously treated with conventional scleral buckling procedures with silicone or Silastic explants, cryopexy (1 with diathermy), and both with and without drainage of subretinal fluid. The distribution of tears is evaluated with reference to the 4 o'clock and 8 o'clock meridia, 2 of the patients having inferior tears with reference to these meridia, all the rest having superior tears (Fig. 3). The significance of these meridia in relation

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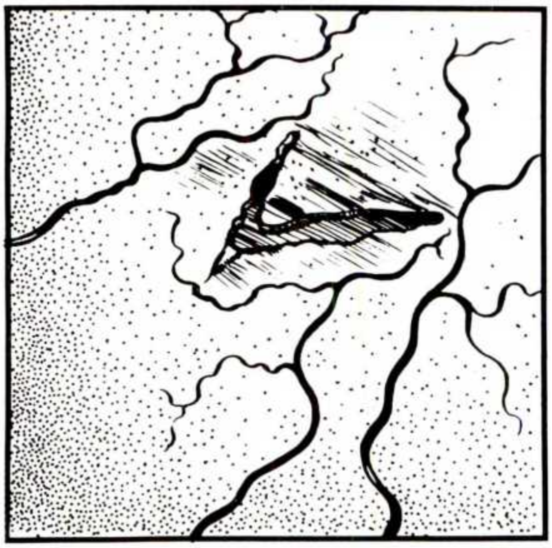

Fig. 1 *Large horsehoe tear in posterior retina showing operculum relatively close to the retinal plane*

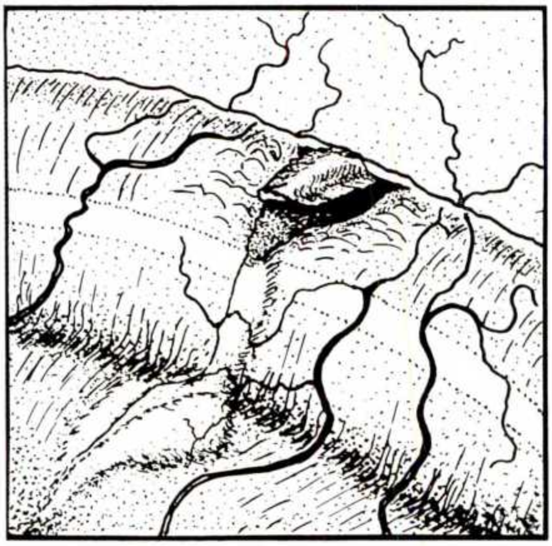

Fig. 2 *Same large horseshoe tear as in Fig. 1 after circumferential scleral buckle has caused reduction in width of tear with elevation of operculum and increase in radial retinal fold*

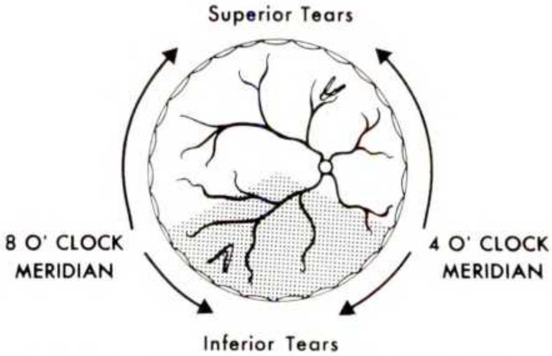

Fig. 3 *In primary detachment procedures all patients with tears in the inferior shaded area have either an augmented intravitreal air technique with scleral buckling or straightforward scleral buckling. With tears in the superior nonshaded area intravitreal air is used without scleral buckling*

to the use of intravitreal air to float the retina up against the cryocoagulated choroid and scleral bed in detachment surgery has been indicated in a previous paper (Chawla and Birchall, 1973). After routine evaluation patients undergo surgery, and all encircling tapes and explants are removed at the outset. Areas of previous cryopexy are noted, and any areas in the vicinity of the tear(s) that have not been frozen are treated together with the area immediately over the tear(s) and a wide surrounding area equivalent to 1 ring of cryo applications external to any previous cryopexy. Subretinal fluid is released by scleral scratch incision and choroidal puncture at a point distant from the tear(s), and in an area of high detachment inferiorly if possible, where any dependent fluid collects. Care is taken not to drain fluid in the equatorial meridian.

With the eye potentially hypotonic the intraocular tension is maintained by means of pressure externally from a cotton-tip applicator, and a pars plana injection of sterile air is made into the vitreous cavity. The intraocular tension is maintained and the injection is discontinued while the eye is still soft.

A no. 40 silicone tape is placed beneath the insertions of the rectus muscles and the ends are secured with a tantalum clip. This tape is then slowly moved posteriorly until it reaches the equator and it is secured there in all 4 quadrants with Dacron sutures. When any horseshoe tear(s) is straddling the equator the no. 40 tape is secured in that quadrant posterior to the tear. The tape *does not* indent over any tear(s), and *no* implant or explant is used to buckle the sclera.

After the operation the patients are positioned in bed, and when possible in bedside chairs, so that the intravitreal air covers the site of the tear(s) internally. In the 2 patients with inferior tears positioning the air bubbles in the vitreous to cover the tear(s) required them to lie flat, without pillows, with the foot of the bed slightly raised. This position was maintained for 48 hours in 1 patient and 72 hours in the second. Depending on the volume of intravitreal air used the air bubbles re-absorb in 5 to 9 days.

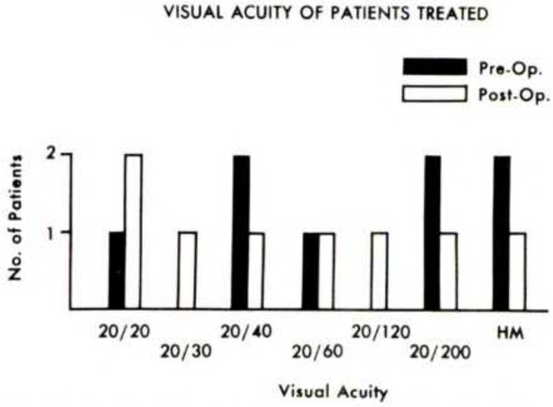

Fig. 4 *Preoperative and postoperative visual acuities of 8 patients with secondary fishmouth phenomenon detachments treated with intravitreal air technique*

Results

In this series 8 patients were treated in the above manner. Two of the patients had inferior tears as defined. Four patients had macular detachments of unknown duration, but none had any clinically appreciable vitreous retraction. All the patients had anatomical reattachment of the retina with 1 operation by the method described above. Complications were remarkably few despite the fact that the patients had previously undergone detachment surgery with scleral buckles. One patient suffered an operative complication. This was a small subretinal haemorrhage from the site of choroidal puncture, but postural treatment prevented it from reaching the posterior pole.

The best postoperative visual acuity of the 4 patients with macular detachments was 20/120 pt (6/36 pt metric), the worst was hand movements at 1 m. In the patients with attached maculae at the time of operation the final visual acuities range between 20/20 (6/6 metric) and 20/40 (6/12 metric). Follow-up time was 6 months to 2 years 3 months (Fig. 4).

Discussion

Many methods of surgical correction for redetachments due to fishmouth formation have been described (Lincoff *et al.*, 1965; Schepens, 1965; Kreiger, 1971; Shea *et al.*, 1972; Pruett 1977) and all include some type of scleral implant or explant. Lincoff *et al.* (1977) in the later part of their series, used gas or air alone in some cases of very large horseshoe tears and they also combined the use of these agents with radial buckling in other cases.

The method described above does not use any buckling implant or explant, and the no. 40 silicone tape is carefully positioned not to indent over the retinal tear(s). The series is small and the results are not statistically significant. This in itself poses some questions.

In a recent article in which the criteria for the production of fishmouthing were examined the expected incidence of the phenomenon was 10% of a series of 560 patients with primary rhegmatogenous detachment (Pruett, 1977). Of the present author's last 90 patients examined preoperatively for *primary* rhegmatogenous detachment 8 patients fulfilled criteria for the subsequent fishmouthing of their retinal tears. However, in practice after detachment surgery only 1 of the 90 patients developed the fishmouth phenomenon. The discrepancy between the expected incidence in the 2 series of patients and the actual incidence in the series of 90 patients may be accounted for as follows. It has been this author's practice to treat all *primary* detachments with superior tears, as defined, by means of an intravitreal air injection, cryopexy, and a no. 40 silicone tape, as previously described (Chawla and Birchall, 1973). Only patients with tears below the 4 o'clock and 8 o'clock meridia have had silicone-guttered explants placed securely beneath the no. 40 tape to buckle the sclera at the site(s) of tear(s). Thus more than 70% of these 90 patients have not had any scleral buckling performed. The 1 patient of this series of 90 who developed a fishmouth phenomenon was in the inferior tear group.

As a point of conjecture it may then be good prophylaxis to treat patients with large horseshoe tears primarily with intravitreal air or gas (Lincoff *et al.*, 1977), cryopexy, and no scleral buckle. Other workers' results suggest this also (Chawla and Coleiro, 1977). The question arises, Why use a no. 40 silicone tape at all? It is thought that the use of such a tape with very minimal tension at or about the equator produces counteraction against any intravitreal retinal traction. As there may be vitreous traction at the rolled edges of large tears one has not yet been bold enough to discontinue its use. Such a method described above without the use of the tape may be the subject of a future pilot study.

The use of secondary cryopexy in previously frozen areas showing good chorioretinal reaction does not cause anxiety. Such secondary treatment does not preclude the production of new adhesive connections both intraretinally, between the rods and villi of the retinal pigment epithelial cells, and subretinally between the pigment epithelium and the collagen layers of Bruch's membrane and choroid. So long as the primary cryopexy does not cause total necrosis of the retinal pigment epithelium then the new cryoadhesions caused by the repeat cryopexy will be as strong as any initial cryoadhesions (Kreissig and Lincoff, 1975).

The use of intravitreal air in retinal detachment surgery is an old concept (Rosengren, 1938) which acquired a dubious reputation because of the occasional incidence of a massive intraocular infection. Modern surgical techniques appear to have eliminated this complication, and the intravitreal air method has now become accepted in many retinal units as part of their regular spectrum of surgical alternatives. Since the incidence of fishmouthing horseshoe tears may be predicted, this intravitreal air technique used in appropriate cases is a satisfactory method of virtually eliminating surgical failure due to the phenomenon. When fishmouthing has inadvertently occurred, the method is a safe and easy way in which to re-attach the retina, leaving the operated eye quiet within a few days of surgery.

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Role of lacrimal scintigraphy and subtraction macrodacryocystography in the management of epiphora

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SUMMARY Fifty-one patients were investigated by subtraction macrodacryocystography (SMDCG, 103 systems) and by lacrimal scintigraphy (LS, 105 systems). It was found that these investigations complemented each other and between them the precise site of obstruction in the lacrimal drainage apparatus could be determined in 80%. The radiation dosage to the lens in SMDCG is significant, and it is therefore recommended that the patients with lacrimal obstruction should: (1) have lacrimal puncta dilated with a probe to No. 1 diameter and be forcibly syringed; (2) have lacrimal scintigraphy performed; (3) if the site of the obstruction is still uncertain, then and only then should SMDCG be performed.

Epiphora can often be managed by listening to the history, examining the lids, and syringing the lacrimal drainage apparatus. However, this will not always determine the site and nature of the obstruction, and further investigations can then be of assistance.

Dacryocystography has been performed since 1909 (Ewing, 1909). The technique was much improved by Lloyd (1973), who used intubation and subtraction macrodacryocystography (SMDCG). This technique enables the lacrimal system to be outlined in detail, but the results are sometimes misleading, particularly in common canalicular obstruction and in patients with a functional block (Demorest and Milder, 1955), that is, patients with epiphora and normal classical dacryocystography.

Rossomondo *et al.* (1972) demonstrated the passage of 99 m technetium through the lacrimal drainage apparatus with a gamma camera and a specially developed micropinhole collimator (Microscintigraphy, Lacrimal Scintigraphy, Lacrimal Scintillography). By this technique the dynamics of the lacrimal drainage apparatus could be studied under much more physiological conditions. Hurwitz *et al.* (1975a) and Chaudhari *et al.* (1974, 1975) have used both the subtraction macrodacryocystogram and lacrimal scintigraphy to assess the lacrimal drainage in patients complaining of epiphora, and arrived at different conclusions.

The purpose of this paper is to assess again the value of these techniques in ordinary hospital practice and to compare them with simple clinical observations in order to determine whether either method should be used to decide the operative procedure. In addition, the effects of those treatments have been evaluated.

Material and methods

All patients who attended the Eye Department of Addenbrooke's Hospital, Cambridge, and Huntingdon County Hospital, Huntingdon, complaining of epiphora over a period of 2 years were included in the study.

All patients had a careful examination to detect any obvious lid abnormalities such as ectropion, eversion of punctum, or entropion. This was followed by syringing of the lacrimal drainage apparatus, subtraction macrodacryocystography (SMDCG), and lacrimal scintigraphy (LS).

The nasolacrimal drainage system was studied bilaterally in 51 patients, except in 1 patient who was 1-eyed and therefore 1 side only was studied. Ten of these were male patients (this included a 3-year-old boy) and 41 were female patients. Two patients had both the SMDCG and LS repeated, 1 patient had the LS only repeated, while 2 patients did not

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Table 1 *Result of dacryocystorhinostomy*

Patient no.	*SMDCG result*		*LS result*	
	Preoperative	*Postoperative*	*Preoperative*	*Postoperative*
4 (R)	NL duct obstruction	DCR patent	Canalicular obstruction	Lacrimal sac obstruction
11 (L)	No obstruction	Free flow	Lacrimal sac obstruction (partial)	Lacrimal sac obstruction
47 (L)	NL duct obstruction	Free flow	NL duct obstruction	Not done
54 (L)	Canalicular obstruction	Canalicular obstruction	Canalicular obstruction	Canalicular obstruction

All patients were asymptomatic except Patient 54. NL = nasolacrimal

Table 2 *Results of dacryocystorhinostomy with silicone tubes*

Patient no.	*SMDCG result*		*LS result*	
	Preoperative	*Postoperative*	*Preoperative*	*Postoperative*
1 (R)	Upper and lower canalicular obstruction	Free flow	Canalicular obstruction	Improved flow
3 (L)	Canalicular obstruction	Canalicular obstruction	Canalicular obstruction	Canalicular obstruction
7 (R and L)	Canalicular obstruction	Free flow	Canalicular obstruction	Good flow
13 (R and L)	Not done	Canalicular obstruction	Canalicular obstruction	Canalicular obstruction
20 (R)	Upper and lower canalicular obstruction	Not done	Canalicular obstruction	Free flow
29 (R)	NL duct obstruction (partial)	Slow but definite flow	NL duct obstruction	Slow but definite flow
35 (R)	Canalicular obstruction	Lacrimal sac obstruction	Canalicular obstruction	Lacrimal sac obstruction
43 (L)	Canalicular obstruction	Free flow	Canalicular obstruction	Free flow
57 (L)	Canalicular obstruction	DCR patent	Canalicular obstruction (partial)	Canalicular obstruction (partial)

All patients were asymptomatic except Patient 13

have an SMDCG. Thus, in all, 103 systems were studied by SMDCG and 105 systems were studied by LS. Most patients who required some form of surgery had SMDCG and LS repeated after the operation, the time interval varying from patient to patient depending on the nature of surgery. The preoperative findings in patients who required a dacryocystorhinostomy (DCR) or a DCR with silicone tubes are compared with those obtained postoperatively, in Tables 1 and 2 respectively. It is of interest to note that although the symptoms were relieved in all but 1 patient, who had dacryocystorhinostomy with silicone tubes, obstruction in the lacrimal drainage system could be demonstrated postoperatively by SMDCG and LS in 2 other systems (Patients 3 and 35). In patients who had dacryocystorhinostomy alone without silicone tubes LS remained abnormal in those in whom it was possible to carry out this investigation. In addition 6 of the 14 patients who improved symptomatically after the investigations had the SMDCG and LS repeated to ascertain any difference in the results of the investigations (Table 3). In 4 patients the obstruction was no longer demonstrable on SMDCG and/or LS.

TECHNIQUE OF LACRIMAL SCINTIGRAPHY

After the procedure has been explained the patient sits erect on a chair in front of the $\frac{3}{16}$-in (4·5-mm) pinhole collimator, with the chin and forehead stabilised on a stand similar to the one attached to a slit lamp. A band is secured around the patient's head to minimise involuntary movements. The distance between the collimator and cornea is approximately 50 mm.

Immediately before the radioactive isotope is instilled the lacrimal sacs are emptied by digital expression and immediately afterwards 15 µl con-

Table 3 *Comparison of results in patients who became asymptomatic*

Patient no.		*SMDCG result*		*LS result*	
		First visit	*Second visit*	*First visit*	*Second visit*
5	(R)	NL duct obstruction	No obstruction	No obstruction	? Partial hold-up at NL duct
9	(L)	Lacrimal sac obstruction	Lacrimal sac obstruction	Canalicular obstruction	Unsatisfactory
17	(L)	NL duct obstruction	No obstruction	NL duct obstruction	Normal
37	(L)	Lacrimal sac obstruction	No obstruction	Canalicular obstruction	Lacrimal sac obstruction
50	(R)	Difficult to cannulate	No obstruction	Normal	Normal
	(L)	No obstruction	No obstruction	Canalicular obstruction	Canalicular obstruction
51	(R)	Normal	No obstruction	Normal	Normal
	(L)	Normal	No obstruction	Canalicular obstruction (partial)	Normal

taining about 50 μCi of 99 m technetium sulphur colloid is delivered simultaneously to the conjunctival sacs at the lateral canthus by means of automatic Finnpipettes. Gama camera data acquisition is started at the same moment. The passage of the tracer is displayed on an oscilloscope, and serial images are recorded at 20-second intervals for 10 minutes on the magnetic disc of a computer system (Varicom-Varian 620L). The data on the magnetic disc are later transferred to a tape. After the study has been completed the data are analysed.

Static views are reproduced on a hard copy showing the pattern of lacrimal flow at 1 to 20 seconds, 21 to 40 seconds, 1 to 2 minutes, 3 to 4 minutes, 5 to 6 minutes, 7 to 8 minutes, 9 to 10 minutes, and a final copy showing the 'sum' view from 0 to 10 minutes.

A suitable view is then displayed on the oscillo-

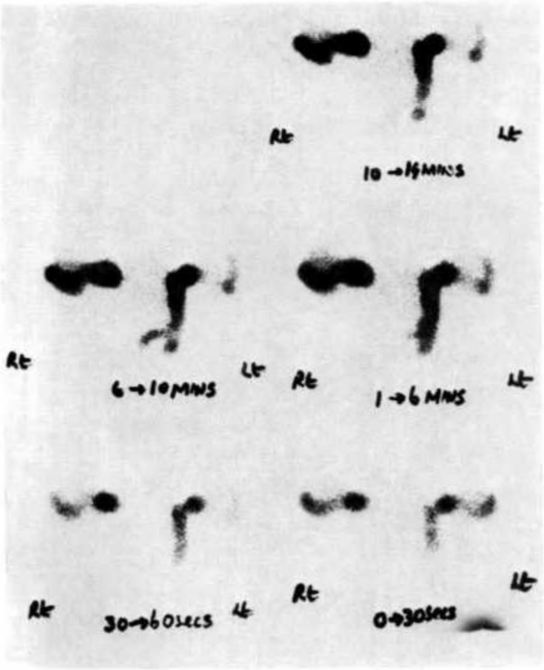

Fig. 1 *Lacrimal scintigram of a patient showing obstruction at canalicular level on right side*

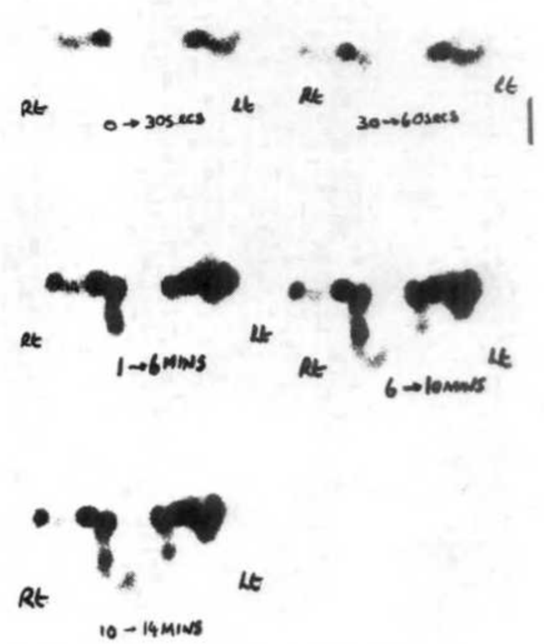

Fig. 2 *Lacrimal scintigram of a patient showing obstruction at lower end of lacrimal sac on left side*

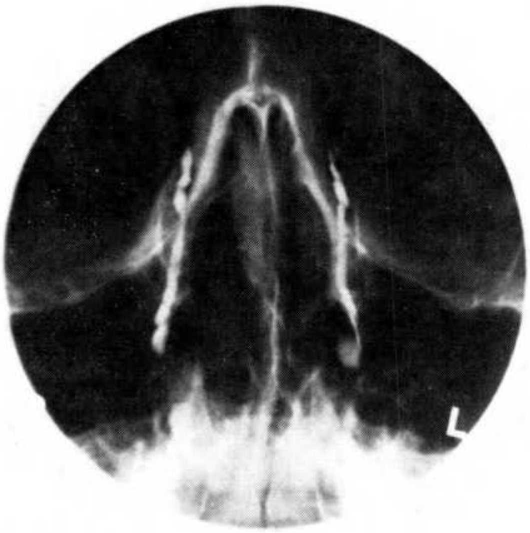

Fig. 3 *Normal macrodacryocystogram of a patient complaining of persistent left epiphora*

scope and 5 areas of interest are defined on each side outlining the conjunctival sac, medial canthus, lacrimal sac, nasolacrimal duct, and the nasal cavity.

Dynamic curves of changes in activity with time in these regions are then plotted by the computer.

The serial images are interpreted in the light of the dynamic curves and assessed for the presence of complete or partial obstruction and the level at which it occurs.

The lacrimal scintigraphy method differs slightly from that used by Hurwitz *et al.* (1975b) in that the sac is expressed before the investigation is started, thus enabling the lacrimal sac to be more readily visualised by emptying it from any accumulated tears.

TECHNIQUE OF SUBTRACTION MACRODACRYOCYSTOGRAPHY

The macrodacryocystography technique used for the examination of the patient in this study was that described by Lloyd (1973). The patient is examined in the supine position with the orbits at a level approximately two-thirds the distance between the tube target and the film to produce an enlarged image of about × 1·5 magnification. The *x*-ray tube has a 0·3-mm focal spot to reduce geometric blur. The lower or occasionally the upper canaliculus is catheterised with a fine nylon tube, and a film for subtraction is taken immediately before the injection of contrast medium. A series of 3 or 4 films are taken during the injection of 1·0 to 1·5 ml of iodised oil (Lipiodol ultra fluid). A positive image of the film taken for subtraction purposes is superimposed on one or more of the films taken during the injection of contrast medium to obtain a bone-free image of the contrast-filled duct system.

Results and analysis

The total number of patients studied was 51. The obstruction in the lacrimal passages was revealed in some by both SMDCG and LS, in some by LS alone, and in some by SMDCG alone as detailed in Table 4. It is interesting to note that, of the 25 patients who had symptoms of epiphora unilaterally, there were 7 patients in whom the opposite asymptomatic eye showed a definite obstruction in the lacrimal drainage apparatus; six of these were

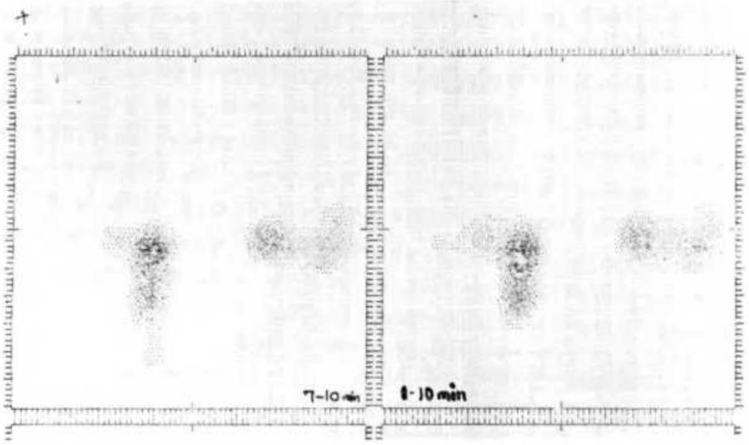

Fig. 4 *Lacrimal scintigram of the same patient as in Fig. 3 showing complete functional obstruction at canalicular level on left side*

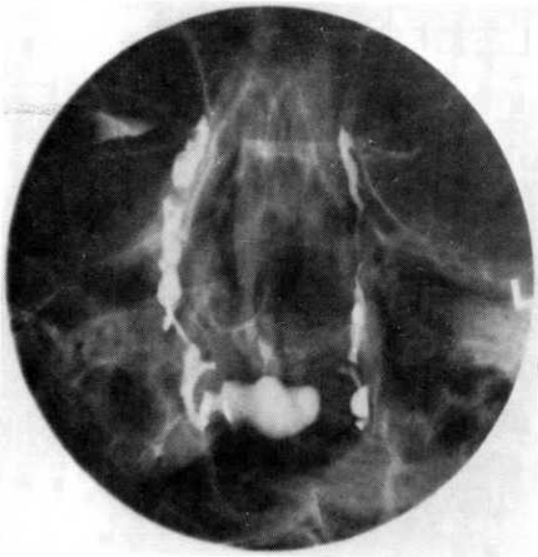

Fig. 5 *Macrodacryocystogram showing stenosis and partial obstruction of right nasolacrimal duct with consequent dilatation of lacrimal sac*

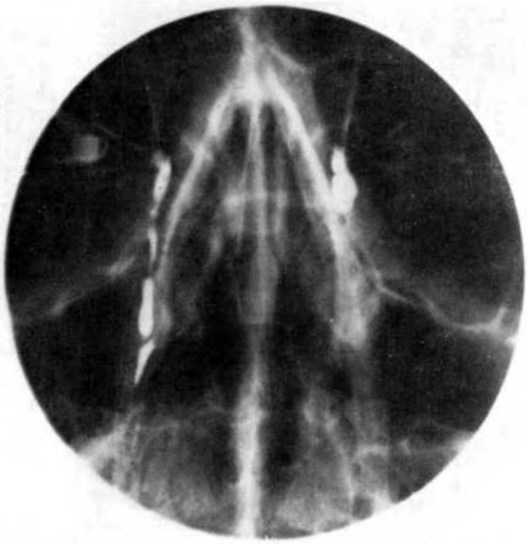

Fig. 6 *Macrodacryocystogram showing obstruction at the lower end of lacrimal sac on left side*

demonstrated by LS alone and one by both SMDCG and LS.

The exact sites of obstruction, as determined by syringing and SMDCG and LS, are compared in Table 5. It is evident from Table 5 that a definite level of obstruction could be determined by syringing in 34 out of 77 systems (44%), by SMDCG in 44 out of 79 systems (55·7%), and by LS in 62 out of 81 systems (76·6%). It should be noted that stasis due to distal obstruction may result in hold-up of tracer more proximally and lead to error in determining the site of obstruction by LS.

Twenty-six patients complained of bilateral epiphora, and 25 patients complained of unilateral epiphora; altogether 81 symptomatic systems were studied in these patients. In 41 systems the obstruction was picked up by both the SMDCG and LS (Table 4, excluding one asymptomatic system); SMDCG alone revealed an obstruction in 3 systems; and LS alone revealed an obstruction in 21 eyes (Table 6, excluding the 6 asymptomatic systems). Thus between them SMDCG and LS were able to demonstrate an obstruction in 65 out of the 81 symptomatic systems (80%).

Discussion

Epiphora is never dangerous and at worst causes excoriation of the skin, but is nonetheless an extremely irritating symptom, made worse by exposure to wind and sun, often preventing the patient from working properly because of the constant streaming

Table 4 *Method by which obstruction was revealed*

(A) *Symptoms of bilateral epiphora present in*	*26 Patients (56 systems)*
(*i*) Bilateral obstruction demonstrated in	14 patients (30 systems)*
By both SMDCG and LS in	17 systems
By LS alone in	13 systems
(*ii*) Unilateral obstruction demonstrated in	10 patients (10 systems)
By both SMDCG and LS in	6 systems
By LS alone in	3 systems
By SMDCG alone in	1 system
(*iii*) No obstruction could be demonstrated in	3 patients (6 systems)†
(B) *Symptoms of unilateral epiphora present in*	*25 Patients (50 systems)*
(*i*) Unilateral obstruction demonstrated in	18 patients (18 systems)
By both SMDCG and LS in	13 systems
By LS alone in	3 systems
By SMDCG alone in	2 systems
(*ii*) Bilateral obstruction demonstrated in	7 patients (14 systems)
Symptomatic	
By both SMDCG and LS in	5 systems
By LS alone in	2 systems
Asymptomatic	
By both SMDCG and LS in	1 system
By LS alone in	6 systems

*One patient had the SMDCG and the LS repeated so that he had 4 systems investigated. †One of these patients had the investigations done twice; on the first occasion she showed a unilateral obstruction only and so this patient is also included in subgroup (ii). In brief: SMDCG and LS together revealed an obstruction in 42 systems, LS alone revealed an obstruction in 27 systems, and SMDCG alone revealed an obstruction in 3 systems

Table 5 *Comparison of site of obstruction*

Level of obstruction	*Syringing*	*SMDCG*	*LS*
Upper canaliculus	—	1	—
Lower canaliculus	4	—	—
Combined upper and lower canaliculus	—	2	—
Complete obstruction of common canaliculus	16	15	27
Partial obstruction of common canaliculus	—	2	4
Complete obstruction of lower end of lacrimal sac	3	7	12
Partial obstruction of lower end of lacrimal sac	—	1	4
Complete obstruction of nasolacrimal duct	11	10	5
Partial obstruction of nasolacrimal duct	—	6	4
Level of obstruction difficult to ascertain	20	—	6
No obstruction demonstrated in symptomatic eyes	18	35	19
Level of obstruction not recorded	5	—	—
	77	79	81
Asymptomatic systems*	—	24	24
Total systems	77	103	105

Syringing revealed an obstruction in 34 out of 77 systems (44%). SMDCG revealed an obstruction in 44 out of 79 systems (55·7%). LS revealed an obstruction in 62 out of 81 systems (76·6%). *Seven of these showed an obstruction in the lacrimal drainage apparatus

of tears on to the face. It is always a great social embarrassment. The patient therefore demands relief, which can usually be effected provided the appropriate treatment is given. This depends on determining accurately the site of obstruction to the outflow of tears from the eye. The tears will overflow from the eye if the lids are lax and allow the punctum to be everted, if either the upper or the lower punctum is everted, if either the upper or the lower punctum is stenosed, if the lumen of the canaliculi are occluded or they are constricted from without by fibrosis or aberrant muscle action, or by the presence of abnormal mucous membrane valves. Even if the tears do enter the lacrimal sac, the outflow from the sac may be obstructed by malformations, infection or damage to the mucous membrane valves of the sac itself. As the abnormalities of the lids and puncta can be dealt with easily by eyelid tightening procedures, retropunctal cautery, dilatation of the puncta, or the permanent opening of the puncta by the three-snip procedure, it is most important to establish that this is the sole site of faulty lacrimal drainage.

Table 6 *Level of obstruction on LS when SMDCG was normal*

Complete canalicular obstruction	5 systems
Partial canalicular obstruction	1 system
Complete obstruction at the lower end of lacrimal sac	10 systems
Partial obstruction at the lower end of lacrimal sac	3 systems
Complete obstruction at nasolacrimal duct	3 systems
Partial obstruction at nasolacrimal duct	2 systems
Total	24 systems

In addition to these 24 systems there were 3 systems which also revealed an obstruction on LS, but as a SMDCG was not done on these they are not included in the Table. The Table includes the 6 systems which were asymptomatic contralateral eyes

Lesions of the lacrimal sac and the outflow mechanisms of the sac are easily dealt with by dacryocystorhinostomy (DCR). However, if the canaliculi are obstructed, more complex procedures have to be considered, the simplest of which is the insertion of silicone tubes into the canaliculi at the time a DCR is performed.

In recent years subtraction macrodacryocystography and lacrimal scintigraphy have been added to the armamentarium of procedures available for the investigation of epiphora. It has been argued that they are unnecessary and that simply syringing the tear ducts will give all the information that is required. This is not borne out by this study. In fact syringing revealed an obstruction in only 44% of those who complained of symptoms, whereas

Table 7 *Follow-up of patients in whom SMDCG was normal*

22 systems were contralateral asymptomatic systems (these include 6 systems in whom LS showed a definite obstruction)

5 systems improved after investigations

16 systems required no treatment as symptoms were not very severe

2 systems are being treated conservatively

9 systems required surgery*

2 systems awaiting a decision as regards treatment

1 system refused treatment

Total 57 systems

*One had DCR, 2 had DCR with tubes, 3 had three-snip operations, 2 had probing, 1 had retropunctal cautery. Three of these patients also showed normal LS, and are included in Table 10 as well

SMDCG and LS used together showed a definite obstruction in 80% of patients.

Lacrimal scintigraphy succeeded in revealing an obstruction in 76·6% of the symptomatic systems investigated, and the exact level of the obstruction could be determined in all but 6 systems (10%) (Table 5). Of the remaining 19 symptomatic eyes, which showed no obstruction, 3 improved symptomatically after the investigations; 10 did not require any treatment, as symptoms were not severe; 1 patient was treated conservatively with zinc sulphate drops; and only 5 systems required surgery (4 three-snips, 1 DCR with tubes); and even in this latter patient there was a suggestion that the obstruction was at the lower punctum because there was difficulty in trying to cannulate the inferior punctum when SMDCG was performed. It can therefore be said that in this series lacrimal scintigraphy not only showed an obtruction to be present in the majority of patients, but also showed its exact site and revealed those patients in whom either no treatment was going to be necessary or only simple surgery would succeed.

Subtraction macrodacryostography demonstrates the lacrimal system well but is unphysiological in that the contrast medium can be forced through under pressure when it would not pass under normal circumstances. Some anomaly was shown in the lacrimal passages in 55·7% of those investigated with SMDCG; the exact site could be determined in all of them (Table 5). Of those in whom SMDCG failed to show an obstruction, 5 systems (9%) improved spontaneously, presumably owing to stretching of the canaliculi during the procedure, and a further 16 (28%) were improved to the extent that no further treatment is contemplated (Table 7). Nine patients (16%) required surgery (3 of these also showed a normal LS and these have been discussed with LS above); 3 of these required some form of DCR; 2 resolved on further probing; and 1 required the puncta replacing against the globe, while 3 had three-snip operations. In some cases there seems to be a marked therapeutic benefit from actually performing an SMDCG, but this could be achieved by using a wider canula or a No. 1 probe when syringing the ducts initially.

Table 4 shows that rather than being mutually exclusive LS and SMDCG complemented each other. In each of the categories investigated the site of obstruction was revealed by one method and not by the other. One reason for this is possibly because the tracer cannot enter the sac if there is no flow through it; but this cannot be a major factor, because at sites within the lacrimal sac and the nasolacrimal duct, where one would expect the obstruction to show up better with the SMDCG, the number detected by either method was much the same; 24 out of 44 (55%) by SMDCG, and 25 out of 62 (40%) by LS. Using the collimator available to us we were not able to distinguish between upper and lower canalicular block on LS, but these can be easily detected by simple syringing and by SMDCG, as indeed can common canalicular block (Table 2). However, LS seems to show up a higher percentage of canalicular block than SMDCG and syringing, which again could be because the tracer cannot pass into the lacrimal sac through which there is no flow. Again, only rarely does this seem to be the case, because in only 6 patients (Table 8) in whom LS suggested common canalicular obstruction was this found not to be present at operation. In another patient a common canalicular block was suspected, but it was found at operation that the lacrimal sac was completely occupied by a yellow cast. There was therefore no flow at all through the system, and this result confirmed the LS findings of no passage of tracer beyond the medial canthus.

It is interesting to note that the SMDCG revealed both a superior canalicular and an inferior canalicular block on that side. In two other similar situations, where LS showed no passage of tracer beyond the medial canthus, the sac was replaced by small fibrotic masses. In another instance the hold-up of tracer at the medial canthus was due to callous formation at the site of a DCR performed in the past.

It was surprising that the findings by the various methods of investigations did not correspond more often. A definite level of obstruction was revealed in 69 systems, by SMDCG and/or LS (Table 4, excluding the 3 systems which show an obstruction on LS but did not have an SMDCG performed), and yet the level of obstruction as

Table 8 *Comparison of LS and SMDCG results with operative findings*

Patient no.	*LS result*	*SMDCG result*	*Operative findings*
4 (R)	Canalicular obstruction	NL duct obstruction	No canalicular obstruction
11 (L)	Partial obstruction of lacrimal sac	No obstruction	No canalicular obstruction
38 (R) (post-DCR)	Canalicular obstruction	NL duct obstruction	No canalicular obstruction
44 (L)	Canalicular obstruction	Not performed	NL duct not canalised found to be thick bone
47 (L)	NL duct obstruction	NL duct obstruction	No canalicular obstruction
54 (R)	Canalicular obstruction	Canalicular obstruction	No canalicular obstruction
1 (R)	Canalicular obstruction	Upper and lower canalicular obstruction	Common canlicular obstruction
2 (R)	Lacrimal sac obstruction	No obstruction	Not available
3 (L)	Canalicular obstruction	Canalicular obstruction	Patent common canaliculus
7 (R)	Canalicular obstruction	Common canalicular obstruction	Common canalicular obstruction
7 (L)	Canalicular obstruction	Common canalicular obstruction	Common canalicular obstruction
13 (R)	Canalicular obstruction	Not performed	Tiny friable lacrimal sac
13 (L)	Canalicular obstruction	Not performed	Fibrotic ill-defined sac
10 (R) (post-DCR)	Canalicular obstruction	Lacrimal sac obstruction	Callous formation at site of previous DCR
18 (R)	Canalicular obstruction	Canalicular obstruction	Common canalicular block
20 (R)	Canalicular obstruction	Upper and lower canalicular obstruction	Sac filled with yellow hardened cast.
28 (R)	No obstruction	No obstruction	No canalicular obstruction
29 (R)	NL duct obstruction	Partial NL duct obstruction	No canalicular obstruction
35 (R)	Canalicular obstruction	Canalicular obstruction	Block at common canaliculus
43 (L)	Canalicular obstruction	Canalicular obstruction	No canalicular obstruction
57 (L)	Partial canalicular obstruction	Common canalicular obstruction	Constricted common canaliculus patent

NL = Nasolacrimal

shown by these two investigations was identical in only 30 systems (43%). Eighteen systems showed the obstruction to be present at canalicular level. In 2 of these the obstruction was partial; in 2 the obstruction was at the lower end of the lacrimal sac; while in 6 systems there was complete, and in 2 partial, obstruction at the level of the nasolacrimal duct. If the SMDCG appears to be normal and the scintigram abnormal this is certainly of significance, and records a functional block. A normal SMDCG may be misleading because contrast medium injected through the lacrimal drainage system will force apart mucous membrane surfaces which would otherwise obstruct the flow. LS was performed after the SMDCG in the 3 patients in whom the obstruction was demonstrable on SMDCG only and not on LS, and it is possible that the SMDCG may have relieved the obstruction, thus explaining the absence of detectable obstruction on the LS.

Indeed, it is interesting that 21 (41%) of those investigated did not require any surgery (Table 9). Of those who did, the method of treatment was determined by the results of the investigations. Patients with nasolacrimal duct and lower sac obstruction had a dacryocystorhinostomy performed. Silicone tubes were inserted into the canaliculi in those who had canalicular obstruction; they were also inserted in one patient who had nasolacrimal duct problems, but surgery of the nasal mucous membrane flaps was regarded as inadequate.

In 7 patients 8 systems (29%) were treated by simple lid procedures and probing (Table 10). All these patients except one had a normal SMDCG but some abnormality on the LS. This is possibly the

Table 9 *Management of patients after investigations*

	3 Patients declined surgery
	2 Patients were considered unsuitable for surgery*
	1 Patient decided to have surgery elsewhere
	2 Patients failed to attend regularly—thereafter no treatment
	5 Patients being treated conservatively
	14 Patients became asymptomatic or epiphora diminished after investigations
	24 Patients required some form of surgery
Total	51

*One patient was too ill to undergo surgery; the other patient had had irradiation to inner canthus for basal cell carcinoma on that side in the past

Table 10 *Details of lid surgery and probing*

Patient no.	*Abnormality on LS*	*Procedure performed*
2 (R)	Lacrimal sac obstruction	Three-snip and retropunctal cautery
11 (R)	Lacrimal sac obstruction	Probing under general anaesthetic
21 (R and L)	Delay in passage of tracer	Bilateral three-snip
22 (R)	No obstruction	Three-snip
33 (R)	Canalicular obstruction	Probing followed by three-snip
40 (R)	Canalicular obstruction	Retropunctal cautery
53 (L)	Canalicular obstruction	Retropunctal cautery

SMDCG was normal in all these patients except Patient 40, where there was a partial obstruction at the level of the lacrimal sac

result of an abnormality of the lacrimal pump mechanism, because most of these patients show improved flow patterns on lacrimal scintigraphy after surgery and have become asymptomatic. Patient 2, in whom the symptoms persisted, required a DCG with tubes because a repeat LS again showed an obstruction at the level of the lacrimal sac. The symptoms of Patient 53 did not improve after surgery.

The radiation dose to the lens in lacrimal scintigraphy depends to some extent on the degree of retention of tracer in the conjunctival sac. It is usually only a few millirads and does not exceed 20 millirads even in severe obstruction. In contrast the radiation in the area of the lens using the standard techniques of SMDCG, in which the tube distance is very short, is about 2 rads; 200 rads to the lens can produce cataractous changes (Merriam and Focht, 1957). Because of this and of the ability of lacrimal scintigraphy to detect the majority of the obstructions, we would recommend that after syringing the tear duct lacrimal scintigraphy is performed. If doubt still remains as to the site of the obstruction, then and only then should macrodacryocystography be performed.

We thank Mrs S. Smith for her invaluable secretarial assistance and Miss K. Smith for typing the paper.

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Anhidrotic ectodermal dysplasia with lacrimal anomalies

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SUMMARY Ectodermal dysplasia and its related disorders may present with ocular symptoms due to involvement of the ectodermal components of the eye. This paper reports a case of congenital anhidrotic ectodermal dysplasia presenting to the ophthalmologist with epiphora due to lacrimal atresia. The embryonic origin of the lacrimal system suggests that lacrimal anomalies in association with ectodermal disorders are commoner than reports indicate. Their management consists in accurate evaluation of the anomaly followed by surgery.

Various forms of ectodermal dysplasia have been reported. They mainly affect the skin and its appendages, but occasionally the ocular structures are involved as well. The commonest ocular complications reported consist mainly of corneal, lenticular, and retinal changes. This paper reports a case of anhidrotic ectodermal dysplasia associated with lacrimal anomalies.

Case report

A 12-year-old girl presented to the casualty department of the Southampton Eye Hospital complaining of epiphora, which was bilateral and present since birth. The patient had already been seen by an ophthalmologist, who diagnosed punctal atresia. Both lower lacrimal papillae were incised, which had been followed by probing. In spite of that procedure, epiphora remained constant.

General examination showed the unmistakable stigmata of anhidrotic ectodermal dysplasia. These included scarcity of hair growth, particularly evident in the scalp, where the hair was scanty, brittle, and fair, with a small patch of baldness over the vertex, and receding hair line (Fig. 1). Sweat and sebaceous glands were entirely absent so that the skin was xerotic and hyperkeratotic, with hyperpigmented creases (Fig. 2). The nails were abnormal (Fig. 3), and the teeth were either absent or deformed. Her general physical development was poor and the height below average for her age.

Ophthalmic examination showed very sparse eyebrows and eyelashes, the lateral two-thirds being almost absent. Gross epiphora was present, leading to skin excoriation. There was atresia of the upper puncta, while the lower ones were incised. Visual acuity was recorded as 6/6 in each eye, and the intraocular pressure was normal. Examination of the corneae, lenses, and retinae failed to reveal any abnormalities.

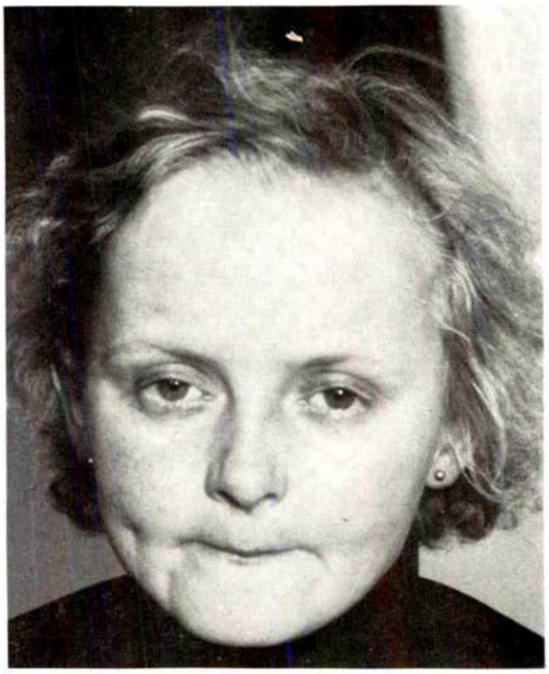

Fig. 1 *Scanty, brittle hair, frontal baldness, sparse eyebrows and eyelashes, hypodontia*

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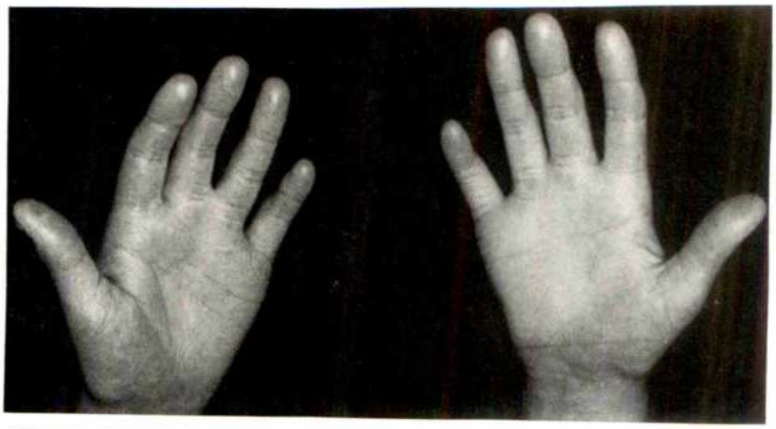

Fig. 2 *Hyperkeratotic skin with hyperpigmented creases*

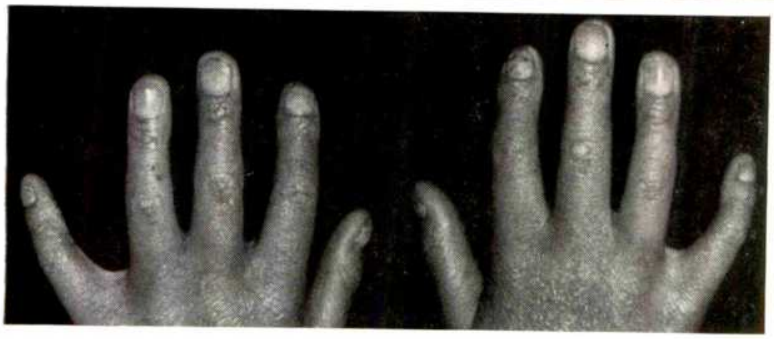

Fig. 3 *Nail anomalies*

Contrast dacryocystography showed the presence of proximal canalicular atresia, the dye failing to enter the lacrimal sac. Surgical exploration followed, which confirmed total absence of upper canaliculus, proximal obstruction of lower canaliculus, and normal sac and nasolacrimal duct. In view of these findings, a dacryocystorhinostomy was performed with canalicular intubation. Two months later the result was satisfactory.

Discussion

Since Wedderhorn (1838) first described anhidrotic ectodermal dysplasia in a Hindu family many similar reports have appeared, mainly in the paediatric, dermatological, and dental literature. Several other hereditary syndromes (Rothmund's, Werner's, progeria, etc.) are closely related to ectodermal dysplasia, all resulting from a maldevelopment of the embryonic ectoderm.

Ocular involvement as one would expect is mainly centred round the ectodermal tissues, although occasionally mesodermal parts of the eye are affected as well. Although Thannhauser (1946) stated that 'none of the numerous cases of ectodermal dysplasia reported in the literature exhibited either cataracts in infancy or in later life', in the following years several authors described congenital cataracts as the commonest ocular complication of ectodermal dysplasia (Gregory, 1955; Mankopf and Hanney, 1957; Marshall, 1958). Other complications include strabismus (Marshall, 1958), corneal anomalies (Kline, 1959; Jung, 1966), Reiger's dysgenesis (Gassler and Berthold, 1960), fibrous tissue in the anterior part of the vitreous, and chorioretinal atrophy (Gregory, 1955).

It is surprising that lacrimal anomalies as a complication of ectodermal dysplasia have only been reported twice, by Mankopf and Hanney (1957) and Beckerman (1973). Embryologically the lacrimal system derives from the surface ectoderm by an original inclusion of a group of cells which forms the sac and subsequently proliferates and canalises to form the canaliculi and nasolacrimal duct. One therefore would expect lacrimal anomalies to be a common complication of ectodermal dysplasia and other related syndromes, but these could easily be missed if such a patient is not examined by an ophthalmologist, who is more aware and better equipped to recognise them. Beckerman also suggests that associated lacrimal gland hypoplasia may reduce the flow of tears and conceal lacrimal drainage problems. In addition, when anomalies are restricted in the upper canaliculus, the functional capacity of the lacrimal draining system is maintained and symptoms are absent.

Thus it is likely that lacrimal complications are commoner than reports suggest but often pass unnoticed as a result of the above-mentioned factors. Their recognition from an ophthalmologist's point of view is important for two reasons: firstly, in the few cases that present first to the ophthalmologist an appreciation of the generalised disorder is necessary to ensure that the patient is referred for further investigation and treatment. Secondly, the treatment of these anomalies follows the pattern of acquired obstructions rather than the customary probing which is the treatment of choice for persistent congenital epiphora. Repeated probings can only prove harmful, and instead dacryocystography should be performed, which will reveal the exact nature of the anomaly. Further management will almost certainly involve surgery, in the form of dacryocystorhinostomy, with or without intubation, depending on the site of the obstruction.

I thank Mr C. B. Walker for allowing me to study his case. I am also grateful to Mr F. Sims for the illustrations and to Mrs J. M. Shapter for secretarial assistance.

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Inequality of the direct and consensual light reflexes in normal subjects

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SUMMARY Anisocoria in darkness and during reflex responses to unilateral light stimulation was studied in 150 normal subjects with television pupillometry. It was commonly found that the direct light reaction of the stimulated eye exceeded the consensual reaction of the other eye. This light-induced anisocoria, termed 'contraction anisocoria', had a mean value of 0·075 mm or 6·1% of light reflex amplitude. The measurement showed a high degree of repeatability in 20 subjects who were tested on two occasions a year apart. It occurred in the presence and absence of prior dark adaptation and increased proportionally with reflex amplitude as the intensity of the stimulating light was raised. It is concluded that, contrary to previous opinion, a small degree of contraction anisocoria is normal.

It is generally accepted that on unilateral light stimulation the direct and consensual light reflexes are of equal magnitude provided there is no lesion in the reflex pathways. However, Lowenstein (1954) described a syndrome, which he called 'alternating contraction anisocoria', in which the direct pupillary contraction of the illuminated eye in response to unilateral light stimulation exceeded the consensual contraction of the contralateral pupil. This light-induced anisocoria was said to be 'alternating' because it varied according to which eye was stimulated. It was said to indicate an abnormality in the reflex pathways because it was found in a third of 'unselected clinical cases' (Lowenstein and Loewenfeld, 1969) but was rarely found in normal subjects. In this paper evidence is presented to show that contraction anisocoria is common in normal subjects, although the extent to which the direct reaction exceeds the consensual is small.

Methods

One hundred and fifty healthy subjects of both sexes, mean age 34·9 years (range 18 to 67 years) who had no history of eye disease volunteered for the study. Vertical pupillary diameters were measured with a Whittaker Corporation Series 1800 binocular infra-red television pupillometer (resolution 0·03 mm) with the subject focusing on infinity. Light reflexes were elicited with light flashes of 100 or 500 ms duration, given every 8 seconds, with the light beam focused to a diameter of 1·8 mm in the plane of the pupil. The light source (Sylvania 2 W tungsten arc lamp) was displaced horizontally to the side of the visual axis, and the angle of incidence so formed was 7° 31′ which resulted in a predominant illumination of the nasal retina. The intensity of the light was varied by insertion of Wratten neutral density filters. Responses of both pupils were recorded on paper and on tape for computer analysis. The amplitude of each reflex and the resting diameter at the foot of the reflex were measured directly from the paper or by computer.

BILATERAL LIGHT STIMULATION

The eyes of 72 subjects were stimulated alternately with 500 ms flashes of light of a standard intensity that gave submaximal pupillary reflex responses (1·0 to 1·5 mm) for this stimulus duration. Three flashes were directed at each eye, and the values for reflex amplitude and resting diameter were averaged.

In order to measure the extent of the contraction anisocoria at different light intensities 18 subjects were dark-adapted by wearing red goggles for 30 minutes prior to testing. For each subject each eye was stimulated with at least 5 light flashes, of 100 ms duration, at 6 light intensities, starting with the lowest. The responses at each intensity were averaged

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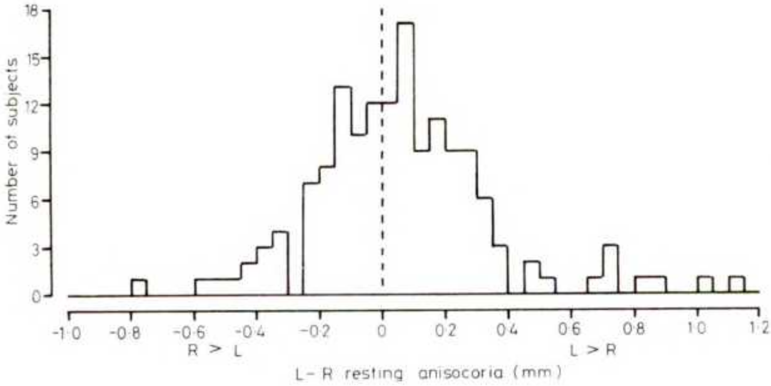

Fig. 1 *Resting anisocoria in 150 normal subjects in the dark*

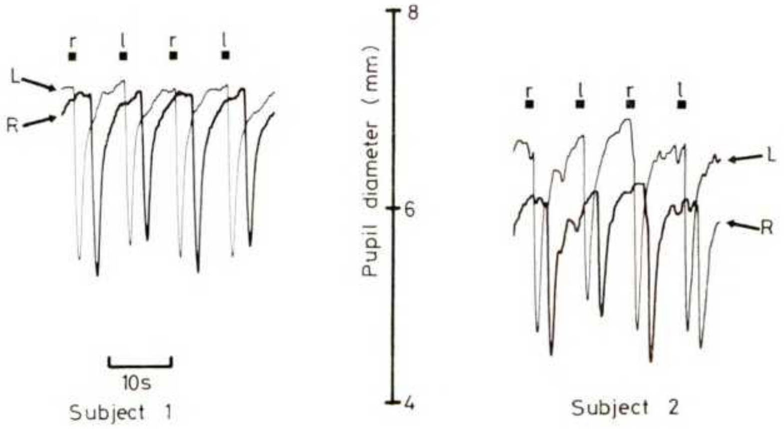

Fig. 2 *Left* (L) *and right* (R) *reflex responses to 0·5 second light flashes directed at each eye (l, r) alternately as indicated. The responses of the 2 eyes are separated on the time axis for convenience. Both subjects have contraction anisocoria (see text for explanation)*

to obtain values for reflex amplitude and resting diameter.

UNILATERAL LIGHT STIMULATION

The left eye of 59 dark-adapted subjects was stimulated with light of an intensity that was adjusted for each individual's visual perception threshold (Fison *et al.*, 1979). Six light reflexes were then elicited with 500 ms flashes of light of an intensity 10^6 times greater than the perception threshold.

Twenty of these subjects were retested approximately 1 year later to assess the repeatability of the measured variables.

Results

RESTING ANISOCORIA

The normal range of resting anisocoria in darkness in all the subjects examined is shown in Fig. 1. The mean (left minus right diameter) for this population was 0·06 mm, which is significantly different from zero ($P < 0·02$). This indicates that there were more people with the left pupil larger than the right pupil than vice versa. However, as the repeatability of the measurement of resting anisocoria was not high (intrapair correlation coefficient $r = 0·56$), this may have been a chance observation. In this population 95% had a resting anisocoria between 0 and 0·7 mm (irrespective of which pupil was larger), and those with larger values were clearly visible in dim light to the naked eye of the observer.

CONTRACTION ANISOCORIA

Three patterns of contraction anisocoria (when the direct reflex exceeded the consensual by more than 0·06 mm, that is, twice the resolution of the pupillometer) were observed on bilateral light stimulation of 72 subjects:

(1) The bilateral form, found in 13 (18·1%) subjects and illustrated in Subject 1 (Fig. 2). When the left eye of this subject was stimulated, the amplitude of the reflex in that eye exceeded the

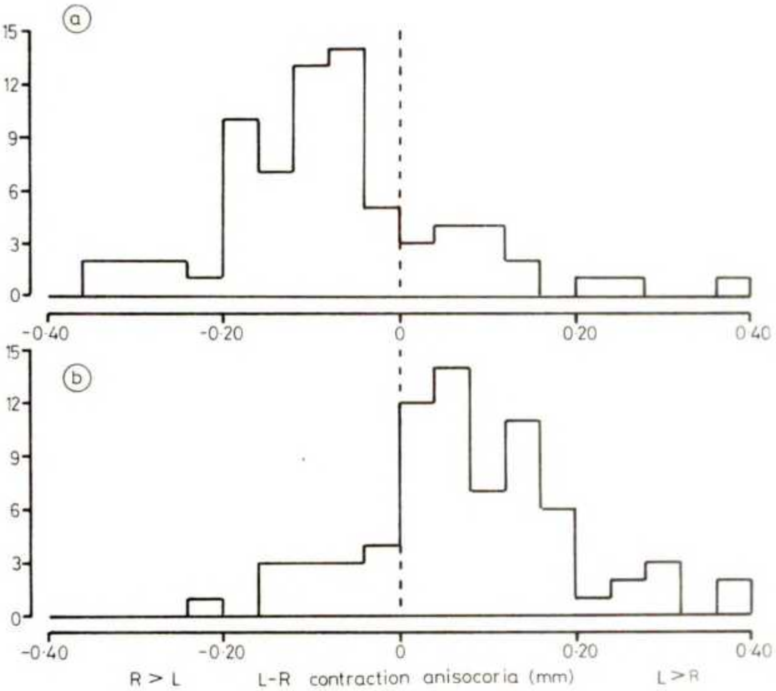

Fig. 3 *Contraction anisocoria in 72 subjects on stimulation of* (a) *the right, and* (b) *the left eye*

right by 0·13 mm, but when the right was stimulated the right pupil contracted 0·11 mm more than the left.

(2) Unilateral contraction anisocoria, in which stimulation of only one side gave a greater direct response and stimulation of the other side resulted in equal reflex responses. This form occurred in 24 (33·3%) subjects.

(3) A further 24 subjects had unilateral contraction anisocoria that differed from (2) in that stimulation of the second eye resulted in the consensual reflex exceeding the direct, such as in Subject 2 (Fig. 2). In this subject the right pupil always responded less than the left irrespective of the side of stimulation, possibly as a consequence of its smaller resting diameter. Thus on stimulation of the right eye the left consensual reflex exceeded the right direct one. However, this subject did have contraction anisocoria, because the amount by which the left reflex exceeded the right was increased from 0·27 to 0·42 mm (or from 16 to 26% of reflex amplitude) on switching the stimulating light from right to left.

There was evidence, therefore, of contraction anisocoria in 84·7% of this group. In no subject did the consensual response exceed the direct one on both left and right stimulation.

Fig. 3 shows histograms of the contraction anisocoria in this population. The mean direct minus consensual difference was 0·07 and 0·08 mm on left and right side stimulation respectively. These values are significantly greater than zero ($P<0·001$) but do not differ significantly from each other. Therefore when left and right side stimulation are considered together, the average contraction anisocoria ($n=144$) was 0·075 ±0·010 mm (mean ± standard error). With each value being taken as a percentage of the average reflex amplitude of the left-right pair, it was found that in this population the direct response exceeded the consensual by 6·1 ±0·8%.

The mean contraction anisocoria resulting from unilateral light stimulation of 59 dark-adapted subjects at an intensity related to individual perception thresholds was 6·8 ±1·2% of reflex amplitude. This did not differ from the mean contraction anisocoria found in the 72 subjects described above who were not dark-adapted. Repeatability of the measurement of the contraction anisocoria obtained in 20 subjects tested on two occasions approximately 1 year apart was high: $r=0·82$.

The absolute degree of contraction anisocoria increased by a small but significant extent with increasing light intensity ($F=3·22$, $P<0·05$) (Fig. 4*a*). Reflex amplitude also increased with intensity ($F=348·6$, $P<0·001$) (Fig. 4*b*), so that contraction anisocoria, when expressed as a percentage of reflex

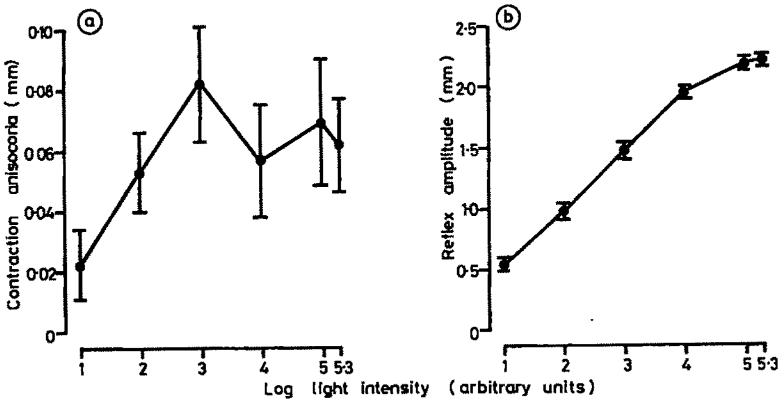

Fig. 4 *The relationship between* (a) *contraction anisocoria and* (b) *reflex amplitude with increasing log light intensity. Means and standard errors* (n = *36) from stimulation of both eyes of 18 subjects are indicated*

amplitude, was not influenced by the brightness of the light.

Discussion

Lowenstein (1954) described the phenomenon of the direct light reflex exceeding the consensual as 'alternating contraction anisocoria'. The term 'alternating' is, however, misleading, because there are subjects in whom the contraction anisocoria does not reverse in direction when the light is switched from one to the other eye. Similarly the term 'consensual deficit' applied to the phenomenon by Thompson (1976) is not a comprehensive description, and we suggest therefore it be termed 'contraction anisocoria'.

Other authors have reported that contraction anisocoria is rare in normal subjects (Jones, 1949; Lowenstein and Loewenfeld, 1969) in contrast to the present study, where it occurred frequently. As the extent of the contraction anisocoria found in our normal population was small (0·075 mm or 6·1% of reflex amplitude) it is possible that it was overlooked previously. Alternatively, it may be that it was even smaller with the brighter, longer light stimuli used by previous workers, although the results from this study (Fig. 4) do not support such a view. Another difference between this and previous studies concerns the position of the light source. In this study it was displaced slightly to the side of the visual axis, so that the nasal retina probably received more illumination than the temporal retina. Others have used larger, centrally placed lights giving more even retinal illumination. It would be interesting to study, therefore, whether discrete illumination of the temporal retina results in the same degree of contraction anisocoria reported here.

It is generally accepted that the supposed equality of the direct and consensual reflexes in man results from an approximately equal distribution of crossed and uncrossed fibres subserving pupillary function firstly in the optic chiasm and secondly in the midbrain. Further, it has been argued that the predominance of crossed fibres at both decussations in cats results in a markedly greater direct pupillary response in this species (Lowenstein *et al.*, 1953). This suggests that the small contraction anisocoria reported here may result from an asymmetry in the decussations similar to, but smaller than that found in cats. There is some evidence that the chiasmal decussation in man may not be completely symmetrical. Kupfer *et al.* (1967) reported that the ratio of crossed to uncrossed fibres was 53:47 in a careful histological post-mortem examination of a case of unilateral enucleation. However, this study has yet to be confirmed, and further, the important anatomical evidence for this hypothesis, at present lacking, is the precise symmetry of the subsequent decussation in the midbrain.

The contraction anisocoria found in these normal subjects was usually too small to be seen without the aid of television pupillometry yet was remarkably consistent in individuals tested on separate occasions a year apart. In contrast, resting anisocoria was more variable with change in the size and even the direction of the anisocoria, a finding in agreement with a previous report (Loewenfeld, 1977). For clinical practice it is important to note, therefore, that the normal occurrence of contraction anisocoria may complicate the diagnosis of subtle pupillary defects by methods such as the swinging-light test (Thompson, 1976).

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British Journal of Ophthalmology, 1979, 63, 528

Book reviews

Handbook of Sensory Physiology. Vol. 9. Development of Sensory Systems. Ed. Marcus Jacobson. Pp. 469. DM230. Springer-Verlag: Berlin. 1978.

Marcus Jacobson asserts in his preface to this volume that 'we have a plethora of facts but a dearth of hypotheses' about the development of sensory systems. This is surely true for neurobiology and biology in general. For the ophthalmologist 2 chapters in this handbook are of direct interest: 'Visual behaviour development in non-mammalian vertebrates' by D. Ingle, and 'Functional modification of the developing visual system' by H. V. B. Hirsch and A. G. Leventhal. The latter chapter is a well-written summary by 2 workers in this exponentially growing field. It covers the organisation of the W, X, and Y systems, and concludes that the W and X systems are invariant, while the Y cell projections are modifiable by the environment. Even if this viewpoint is shown to be oversimplified (and recent work has shown that X-cell properties can be modified by experimental amblyopia), it is pleasing to see the W, X, Y categorisation used to interpret this complex and controversial research area. A. L. HOLDEN

Modern Problems in Ophthalmology. Vol 19. Colour Vision Deficiencies IV. Ed. E. B. STREIFF. Pp. 348. DM198. Karger: Basel. 1978.

Dr G. Verriest, the enthusiastic and indefatigable convener of meetings and editor of symposia, has done it again. The proceedings of Parma '77 of the International Group on Colour Vision Deficiencies have appeared with commendable speed, beautifully produced. The topics covered include neurophysiological aspects, colour vision under reduced illumination, practical (that is, economic and professional) aspects of colour deficiencies, methods of examination, etc. The contributions vary in quality, and the high price (£50) will limit its market. ROBERT WEALE

External Ocular Tumors. By KNUD BECH and OVE ASKEL JENSEN. Pp. 64. £14·00. Holt-Saunders: Eastbourne. 1978.

This is an attractively produced short textbook and atlas recording the clinical, surgical, and radiotherapeutic experience at the Rigshospital and at the Eye Pathology Institute, Copenhagen, which has long had a special interest in the pathology and treatment of ocular tumours. It is based on follow-up of 300 consecutive cases of benign and malignant tumours and of simulating lesions of the external eye as found by inspection of the conjunctiva and eyelids (anterior segment intraocular tumours are by definition excluded).

The various diseases are carefully defined as to their clinical and histological features, which are well shown by juxtaposition of clinical photographs and the corresponding microscopical appearance. The text includes analysis of the history and clinical features and a comparison between the initial clinical diagnosis and the histological diagnosis, pointing out a high error rate in regard to lid papilloma, too often thought to be simple but frequently harbouring a carcinoma, as is often the case with the atypical chalazion. The authors advocate total excision of lesions appearing benign clinically, but for all others where malignancy is suspected a generous biopsy including the margin of the lesion and adjacent skin is done, followed by irradiation. With pigmented lesions of the lids total excision is attempted, followed by major plastic surgery if malignant melanoma is found.

This study emphasises the important principle of careful follow-up of patients with malignant disease, which has been long established in other branches of medicine but is equally important in ophthalmology and clearly justifies the emergence of multidisciplinary ocular oncology clinics. The quality of the black-and-white clinical photographs and microscopical illustrations is excellent and together with the helpful glossary of clinical and histological terms should make this book useful to postgraduate students as well as to those particularly interested in this field. P. A. MACFAUL

Physiology of the Eye. An Introduction to the Vegetative Functions. By IRVING FATT. Pp. 232. £11·10. Butterworths: London. 1978.

This book is apparently designed for optometry students and is intended as an introduction to the purely vegetative physiology of the eye. This restriction being granted, the book is of curiously uneven quality in its approach to the subject, and, while it reflects the author's personal (and extremely valuable) contribution to biophysical problems encountered in the eye, it should not be regarded as an adequate introductory text. The unevenness is nowhere better displayed than in comparing chapters 5 and 6 on lens and cornea; the lens occupies a mere 8 pages as compared with 96 on the cornea. It is difficult to imagine a student who is capable of following the account of corneal oxygen supply under contact lenses (pp. 134–160) and at the same time needs to be informed that 'opacity of the lens, called a *cataract*, is one of the leading causes of loss of vision in the aged' (p. 90). A similar criticism could be made of chapter 8, which devotes the whole of 10 pages to the retina, and even if the author is deliberately refraining from discussing the purely visual functions of that tissue the reader will wish to know something of its vascular supply.

However, let us make the most of what is presented. Chapters 1 and 2 are not inadequate, but chapter 3 seems to give undue prominence to tonographic methods, especially since the reader is told (p. 67) that the 'optometrist never does tonography and the ophthalmologist rarely makes the measurement'. The chapter on cornea (chapter 6) is too detailed for the average student, and after being promised (p. 12) that 'the innervation of the cornea and sclera will be treated in detail in chapters 6 and 7' it is disappointing to find no discussion, either here or in chapter 9 (Tears and Lids), of the nerve pathways involved in the blink and lacrimation reflexes. The present reviewer would also have included the pupillary and accommodation reflexes in the ambit of 'vegetative physiology'. Chapter 6 contains a useful account of the author's own work on the cornea and is an excellent guide to current thinking on the biophysical properties of this tissue, though one would have expected some mention of the techniques of specular microscopy.

To summarise: while this book provides a number of valuable insights, its emphasis is biophysical rather than physiological, and it is insufficiently comprehensive to be regarded as an adequate students' text. D. F. COLE

Genetics and Ophthalmology. GREGORY KEITH. Pp. 116. £9·00. Churchill Livingstone: Edinburgh. 1978.

This concise, accurate, and easily readable book should be welcomed by ophthalmologists, particularly those in training, who will find it a useful guide to the many genetically determined disorders affecting the eye. The short descriptions of the various abnormalities and their modes of inheritance are supplemented by useful references and suggestions for further reading at the end of each chapter. The reader is assumed to have a basic knowledge of human genetics, and few of the many disorders are illustrated. This book must therefore be used in conjunction with a large textbook of ophthalmology or with original papers. But it is none the less an extremly useful addition to the residents' library.

BARRIE JAY

Alles über grünen Star. Fragen und Antworten für Kranke mit Glaukom. By WOLFGANG LEYDHECKER. Pp. 55. DM9·80. Georg Thieme Verlag: Stuttgart. 1978.

Professor Leydhecker has produced a useful handbook which answers various questions on glaucoma. The text is designed to be read by junior medical staff and patients alike and is well illustrated with diagrams and photographs. It is the sort of book that makes easy reading and is informative without oversimplification. If British patients begin to show the same interest in their disease as their counterparts in the United States this book may well perform a useful service in the management of this complicated disease. T. J. FFYTCHE

Do You Really Need Eye Surgery? 2nd edn. By WILLIAM H. HAVENER. Pp. 88. $4·50. Charles C Thomas: Springfield, Illinois. 1977.

This booklet is designed to answer the layman's questions and fears about eye problems and in particular about proposed eye surgery. Such books are difficult to write—to be comprehensive without being corny, to be neither dull nor dramatic and, most of all, to give balanced advice, when the subject is beset with dotty folklore and misconceptions furthered by commercial interests or by excessively lauded and often damaging 'new' techniques. In fact the presentation is impeccable. The risks and costs of fancy new methods are set in their true perspective; the counsel is wise throughout. The patient who is intelligent enough to have recourse to this book will have the reward he deserves, while the others will go on relying on cocktail chat, fashion, and journalistic forays until the damage is done. P. D. TREVOR-ROPER

Symposium on Strabismus. Transactions of the New Orleans Academy of Ophthalmology. By E. M. HELVESTON, A. JAMPOLSKY, P. KNAPP, K. W. McNEER, M. M. PARKS, R. D. REINECKE, W. E. SCOTT, AND G. K. VON NOORDEN. Pp. 608, £38·25. Mosby: St. Louis. 1978.

This symposium is up to the usual high standard that we expect from the New Orleans Academy of Ophthalmology. In addition to reviews of current concepts in amblyopia there are useful contributions on sensory testing, which has always been the non-dominant side of American strabismology. The more usual emphasis on surgical techniques is well represented here, with particular reference to mechanical and cicatricial causes of strabismus and their treatment. Basic surgical methods are discussed and also the newer procedures of adjustable sutures, and the 'Fadenoperation' is considered. Although most chapters are of less than 20 pages, Dr Jampolsky gains an increasing share of the total with articles of 8, 25, 29, and finally 134 pages. However, his last chapter, an interesting comparison of unequal visual inputs in animals treated as for strabismus in man, is thought-provoking, though discursive, and while not to be accepted uncritically, well worth reading.

The final 100 pages are devoted to round-table discussions and questions presented in their colloquial entirety. If ruthless but responsible editing is regarded as outmoded, then I would urge that in future this section be omitted completely and cassettes of the tape-recorded discussion provided for those who insist on this form of verbose instruction. PETER FELLS

Advances in Ophthalmology. Vol. 37. Ophthalmic Microsurgery. Ed. M. J. ROPER-HALL, H. SAUTTER, and E. B. STREIFF. Pp. 228. DM118. S. Karger: Basel. 1978.

This book is a collection of papers presented at a microsurgical workshop held in Singapore by the Royal Australasian College of Surgeons. Many specialities were represented, but by far the greatest contribution was from ophthalmologists.

The first part of the book will be of great use to a beginner in microsurgery. It has chapters and detailed discussions on the selection of a microscope and the various attachments that are now available (there is a notable lack of this information in the ophthalmic literature). The chapters span the use of simple microscopes for underdeveloped countries to the stereovideo microscope. There are chapters on instruments for microsurgery, the care of these instruments, and their uses, though sometimes one has to read the discussions to get the authors' views about ideal modifications to the microscope such as working distances. One section is devoted to ophthalmological microsurgery, which is fairly comprehensively covered, though vitreous surgery is not given much space. There are small chapters on the Kloti and Girard instruments and a useful chapter on surgery for postoperative astigmatism. Intraocular lenses are mentioned but not in any great detail.

The last part of the book is on otolaryngology, neurosurgery, and vascular and limb implantations. It is short and quite interesting to read.

The main value of this book is in the first part, where the basic principles of microsurgery are discussed in detail. The ophthalmic information available in the second part is all easily available elsewhere. It is a worthwhile addition to the library of a beginner in microsurgery and will also be of interest to the established microsurgeon. BRUCE MATHALONE

1977 Year Book of Ophthalmology. Edited by WILLIAM F. HUGHES. Pp. 384. £17·75. YB Medical Publishers: London. 1977.

This 1977 volume has recently made its appearance and as usual compresses the important literature in ophthalmology over the year into a relatively small space, condensing the reports of new work in a precise form. The text opens with 45 questions addressed to the clinician, and if any reader has doubts about the value of the *Year Book* he has only to discipline himself to answer the 45 questions without reference to the text.

S. J. H. MILLER

Pseudophakos. By NORMAN S. JAFFE, MILES A. GALIN, HENRY HIRSCHMAN and HENRY M. CLAYMAN. Pp. 245. £32·20. Mosby: St. Louis. 1978.

A book on this still somewhat controversial subject has long been needed to serve as an authoritative guide to surgical and clinical practice both for those already involved in it and also for those inclined to take an interest in it, including postgraduate students in ophthalmology. This text fulfils its role excellently, providing a safe and sensible surgical outlook and covering the subject in all its aspects. Sixteen chapters cover theoretical aphakic and implant optics, history, implant chemistry, clinical guidelines, methods of estimating implant power, sterilisation, surgical techniques, complications, and results. All these subjects are generously illustrated with both monochrome drawings and photographs.

The authors have confined themselves to considering implants supported by the iris and/or the posterior lens capsule, to which their own experience has been confined. A chapter by Choyce has been included on anterior chamber lenses. This chapter differs significantly in clinical style from the remainder of the book, but the views expressed are of interest. No mention is made of the 'UGH' syndrome (uveitis, glaucoma, and hyphaema) which has appeared recently in the American literature.

This is a useful and much needed contribution to ophthalmic literature which can be warmly recommended to those interested in the subject. ARTHUR D. MCG. STEELE

Notes

Keeler award for clinical study

The Keeler award for clinical study was founded through the generosity of Keeler Holdings Ltd., by Mr Charles Keeler, who was at that time the chairman and managing director. Its object is to encourage consultant ophthalmologists, senior registrars about to take up consultant appointments, and any other applicants the trustees consider suitable, to visit other centres in the United Kingdom and abroad to gain experience of new techniques. In view of the increasing costs of travel and living expenses, the trustees have decided to create additional travelling fellowships of up to £2000 in any one year. Further information and application forms may be obtained from the Keeler Award, c/o Angus, Campbell & Co., Metropolis House, 39–45 Tottenham Court Road, London W1P 0JL.

Microsurgery course

The Department of Clinical Ophthalmology of the Institute of Ophthalmology will be conducting a course in ophthalmic microsurgery on 24–26 October 1979. It will be a practical course concerning common intraocular surgical procedures. The fee is £80·00 and the closing date for applications is 21 September 1979. Application forms and further details from Mrs P. M. Usher, Microsurgical Course Secretary, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD. A further microsurgical course will be held in the spring of 1980.

Paediatric ophthalmology group

This interdisciplinary study group on paediatric ophthalmology was founded by Dr R. Mac Keith. It includes ophthalmologists, paediatricians, neurologists, psychologists, teachers, social workers, and others involved in the care of visually handicapped children. Its objectives are to further knowledge of the subject, exchange ideas, and stimulate interest in this field to the eventual benefit of children who are visually handicapped. The group meets twice a year—in the autumn at the Newcomen Centre, Guy's Hospital, when formal papers followed by discussion are presented, and early in the year, when visits are made to research units, special schools, or any department involved in the problems of paediatric ophthalmology. The present convener is Dr Neil Gordon, Booth Hall Children's Hospital, Blackley, Manchester, and the organisation of the group is supported by the Spastic Society.

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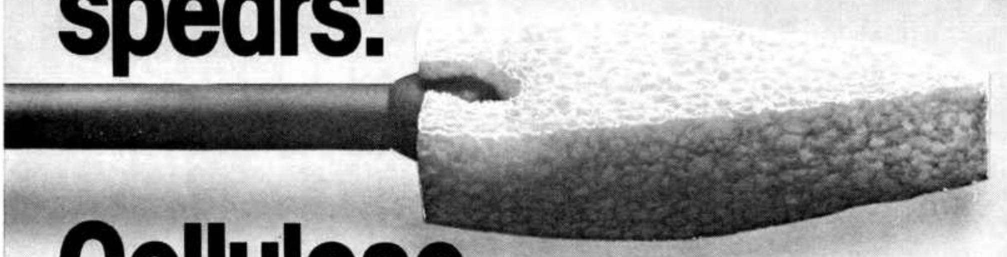

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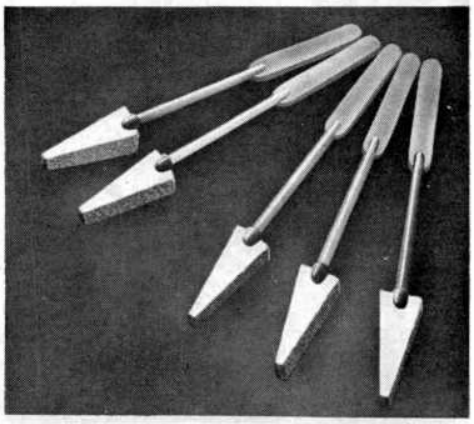

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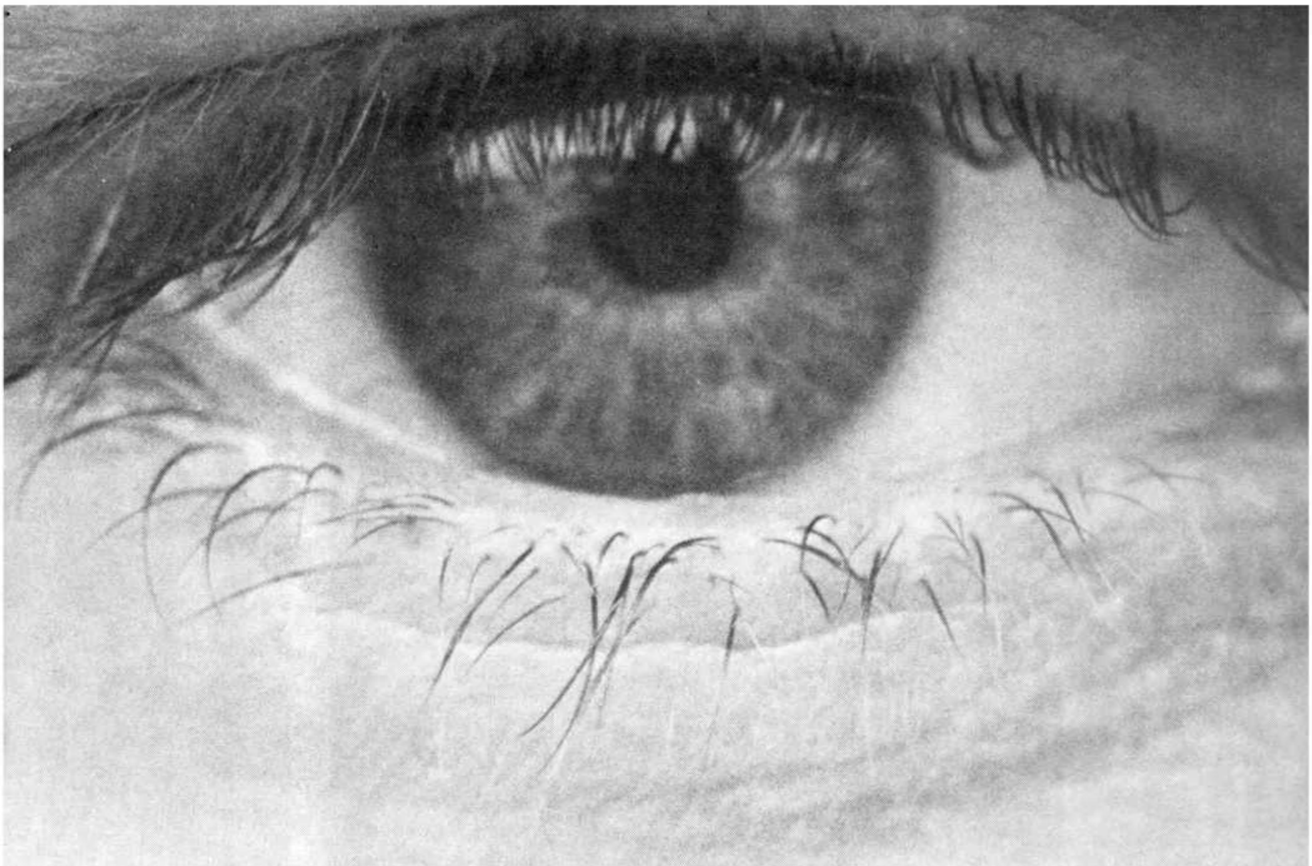

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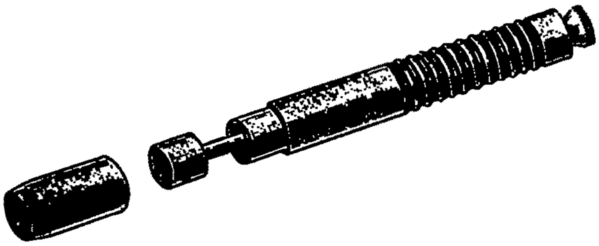

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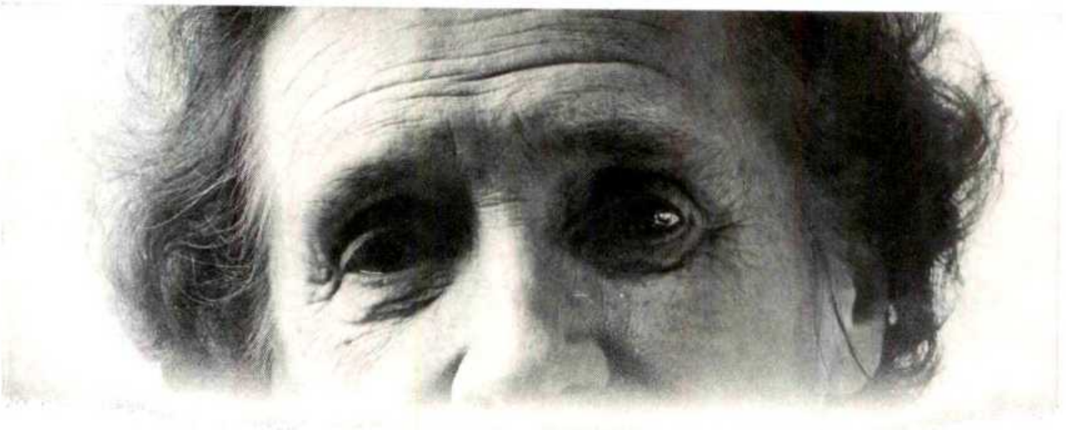

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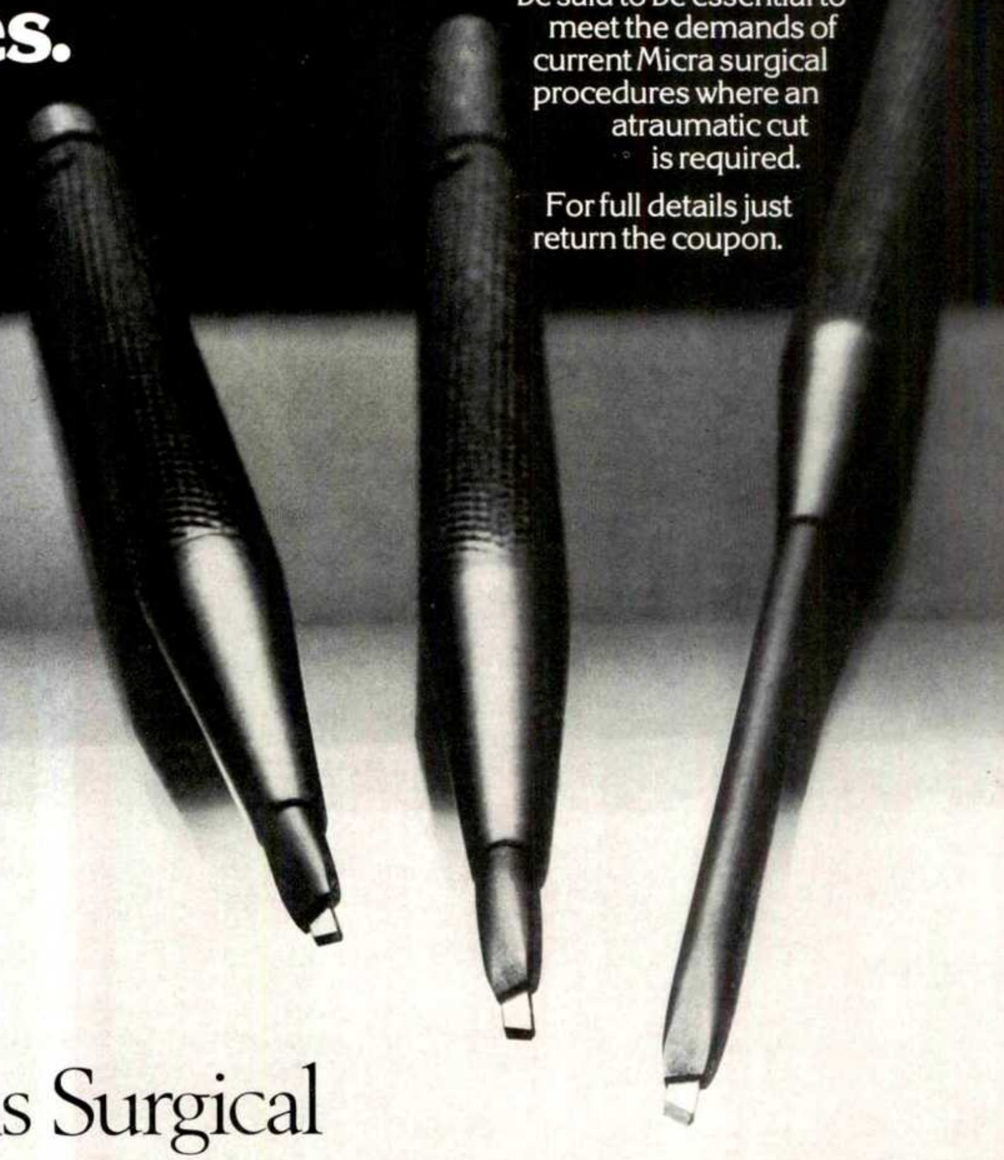

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British Journal of Ophthalmology, 1979, **63**, 531–532

Editorial: Ultrasonic investigation

The eye is a small superficial organ which readily lends itself to ultrasonic investigation. Such examination is indicated when opaque media prevent visualisation of the posterior segment of the globe or if orbital pathology is suspected. Standard 'pulse-echo' techniques are used. Pulses of sound are transmitted into the eye from a transducer, and in the time interval between pulses, echoes are received by the same transducer and recorded. Although a variety of techniques has been employed (Coleman *et al.*, 1969; Coleman and Weininger, 1969; Ossoinig, 1974; Restori and Wright, 1977; Restori, 1978) only A- and B-scan techniques are in routine use. Ultrasonic frequencies suitable for ophthalmology range between 5 and 20 MHz.

First reports of the A-scan technique appeared in the 1950s (Mundt and Hughes, 1956; Oksala, 1958). The transducer is generally coupled directly to the anaesthetised eye by means of methyl cellulose. The echoes are recorded as spikes on a cathode ray tube; the height of the spike indicates the amplitude of the echo, and the position of the spike along the horizontal axis is a measure of the arrival time of the echo at the transducer. The normal A-scan appearances are well known, and diagnosis is made on the basis of the position, the extent, the amplitude, and the movement of abnormal echoes together with the sound-attenuating properties of the abnormality. Some workers place great stress on accurate measurement of abnormal echo amplitudes (Ossoinig, 1974); however, the amplitudes of echoes from large interfaces, such as membranes, are highly dependent on inclination, making quantification tedious.

The use of the B-scan technique in ophthalmology was first described by Baum and Greenwood (1958). The sound is coupled to the eye either by a saline bath or by means of a gel applied to the closed eyelid. The echoes are displayed as spots, the brightness of which indicate the echo amplitude. The transducer is moved to many positions across the eye, and a whole series of intensity registrations are recorded. The resulting B-scan displays a cross-sectional image through the eye and orbit as illustrated by McLeod and Restori on page 533 of this issue.

The transducer may be moved across the eye in a straight line to produce a *linear* B-scan or it may be rocked through an angle to produce a *sector* B-scan. Many of the commercially available B-scanners are of the sector type. Linear and sector B-scans present only partial outlines of the globe, so the eye must be examined in many directions of gaze. Alternatively, a more complete outline of the globe may be achieved by combining the linear and sector transducer movements (*compound* B-scan). B-scans are generally taken in the horizontal plane at regular intervals.

The transducer may be moved manually or mechanically to produce a B-scan. Alternatively, an array of transducers or transducer elements may be fired electronically in sequence to simulate a linear-moving transducer (linear array) or a sector-moving transducer (phased array) respectively. Rapid B-scanning (Bronson, 1974; McLeod and others, 1977) permits dynamic studies of abnormalities in 2 dimensions and thus greatly enhances the recognition and interpretation of such structures. A full lateral deviation of the eye takes approximately 0·1 second, while aftermovements of abnormalities, for example of a detached vitreous gel, are considerably slower (of the order of 1 second). Thus, B-scanners with frame rates in the region of 8 B-scans per second have sufficient time resolution to resolve any such aftermovements. Improving the time resolution on the B-scan by faster scanning, however, has the advantage of reducing flicker on the display and permits easy recording on to standard cine or video systems.

Diagnosis with B-scanning depends on the qualitative recognition of patterns, based on the location, the distribution, the number, the amplitude, and the movement in 2 dimensions of the abnormal echoes. In addition, the sound-attenuating properties, determined by changes in appearance of deeper structures, may aid in the identification of a lesion. Many workers are still using the A-scan technique as a sole means of examination. Others combine the B-scan and A-scan techniques, using the B-scan to provide topographical information and the A-scan to quantify the amplitudes of abnormal echoes. This need for A-scan reflects the unsatisfactory grey scale on most commercially available B-scanners. In the near future as many of the technical problems associated with arrays are overcome it is expected that a selection of high-quality grey-scale, rapid ophthalmic B-scanners will become available.

Much research is now being directed into rigorous analysis of scattered echoes (Lizzi *et al.*, 1976), and the use of computers in this field is expanding. Computers are also being used to generate acoustic images from pulse-echo data. Both of these techniques may improve the accuracy of ultrasonic diagnosis in ophthalmology.

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British Journal of Ophthalmology, 1979, **63**, 533-538

Ultrasonic examination in severe diabetic eye disease

DAVID McLEOD AND MARIE RESTORI

From the Department of Ultrasound, Moorfields Eye Hospital, City Road, London

SUMMARY B-scan ultrasound of the posterior segment is reported in 154 patients with severe diabetic eye disease. Epiretinal fibrosis, vitreous haemorrhage, vitreous detachment, and retinal detachment were frequently diagnosed. The ultrasonic findings are discussed in relation to the pathological changes in the vitreous in proliferative diabetic retinopathy.

Diabetic retinopathy is a common cause of blindness, visual loss resulting from macular oedema, vitreous haemorrhage, retinal detachment, rubeotic glaucoma, or major ocular vascular occlusion. Treatment of certain types of severe diabetic eye disease is now possible with the advent of new techniques of vitreous removal. In planning surgery ultrasonic evaluation is invaluable if the ocular media are opaque (Coleman, 1972; Jack *et al.*, 1974), but no comprehensive report of the ultrasonic findings in diabetes has been published. In this paper we present our results in the last 154 consecutive diabetic patients examined in the Department of Ultrasound at Moorfields Eye Hospital.

Materials and methods

A rapid B-scan technique was used to examine 176 eyes of the last 154 patients referred for ultrasonic evaluation because of severe diabetic eye disease. Of these patients 63 were female and 121 were over 40 years of age.

Table 1 *Prevalence of ultrasonic abnormalities in 176 eyes*

Vitreous haemorrhage	Intragel echoes	101/176 (57%)
	Retrohyaloid echoes	86/176 (49%)
	Both intragel and retrohyaloid	53/176 (30%)
	Not detected	42/176 (24%)
Epiretinal fibrosis	Detected	74/176 (42%)
Vitreous detachment	Diagnosed by compartment echoes	107/176 (61%)
	Diagnosed by interface echoes	149/176 (85%)
	Both compartment and interface	89/176 (51%)
	Not detected	9/176 (5%)
	Predominantly rigid interface	91/167 (55%)
	Predominantly mobile interface	64/167 (38%)
	Compaction sign (ochre membrane)	12/167 (7%)
	Complete vitreous detachment	17/167 (10%)
	Incomplete vitreous detachment	150/167 (90%)
	Localised vitreoretinal adhesion	40/150 (27%)
	Extensive vitreoretinal adhesion	72/150 (48%)
	Multiple vitreoretinal adhesions	22/150 (15%)
	Partial detachment/unclassified	16/150 (10%)
Retinal detachment	Detected	100/176 (57%)
	Localised detachment	82/100 (82%)
	Subtotal/total detachment	18/100 (18%)
	Subretinal echoes	10/100 (10%)

The equipment used and the method of examination were described in previous publications (McLeod *et al.*, 1977; Restori and McLeod, 1977), so only the most salient features are mentioned here. A 10 MHz focused transducer was coupled to the anaesthetised eye by a saline bath, and a Barraquer speculum was used to give good global exposure. The B-scan level could be adjusted remotely by 2 buttons close to the display tube. B-scan sections were normally observed in the horizontal plane at 1 mm intervals with all directions of gaze. Dynamic studies were performed by observing movements of abnormalities on the B-scan during and following a change in direction of gaze. Good grey scale on the B-scan display obviated the need for A-scan studies in most cases. The tonal quality of the Polaroid prints selected for publication is not representative of that observed directly on the display screen.

Results

Vitreous haemorrhage, epiretinal fibrosis, posterior vitreous detachment, and retinal detachment could be diagnosed by ultrasonic examination. Table 1 presents the prevalance of these abnormalities in our series.

Haemorrhage within the vitreous cavity gave rise to scattered point-like echoes of varying amplitudes (Figs. 1a, b, c). Arrangement of such echoes

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to form intragel membranes was sometimes observed (Figs. 1d, e), while sedimentation of haemorrhage within fluid vitreous produced a flat sheet ('fluid-level') of very high amplitude echoes (Figs. 1f, g). If a sheet of high amplitude echoes lower in amplitude than sedimented blood but showing more internal structure was detected on the retinal surface, the echoes were considered to arise from epiretinal fibrous tissue (Fig. 1h).

Posterior vitreous detachment was sometimes indicated by the presence of point-like echoes confined to the gel compartment or retrohyaloid space (Figs. 1a, b, d, i, j). The distinction between these compartments was often emphasised during

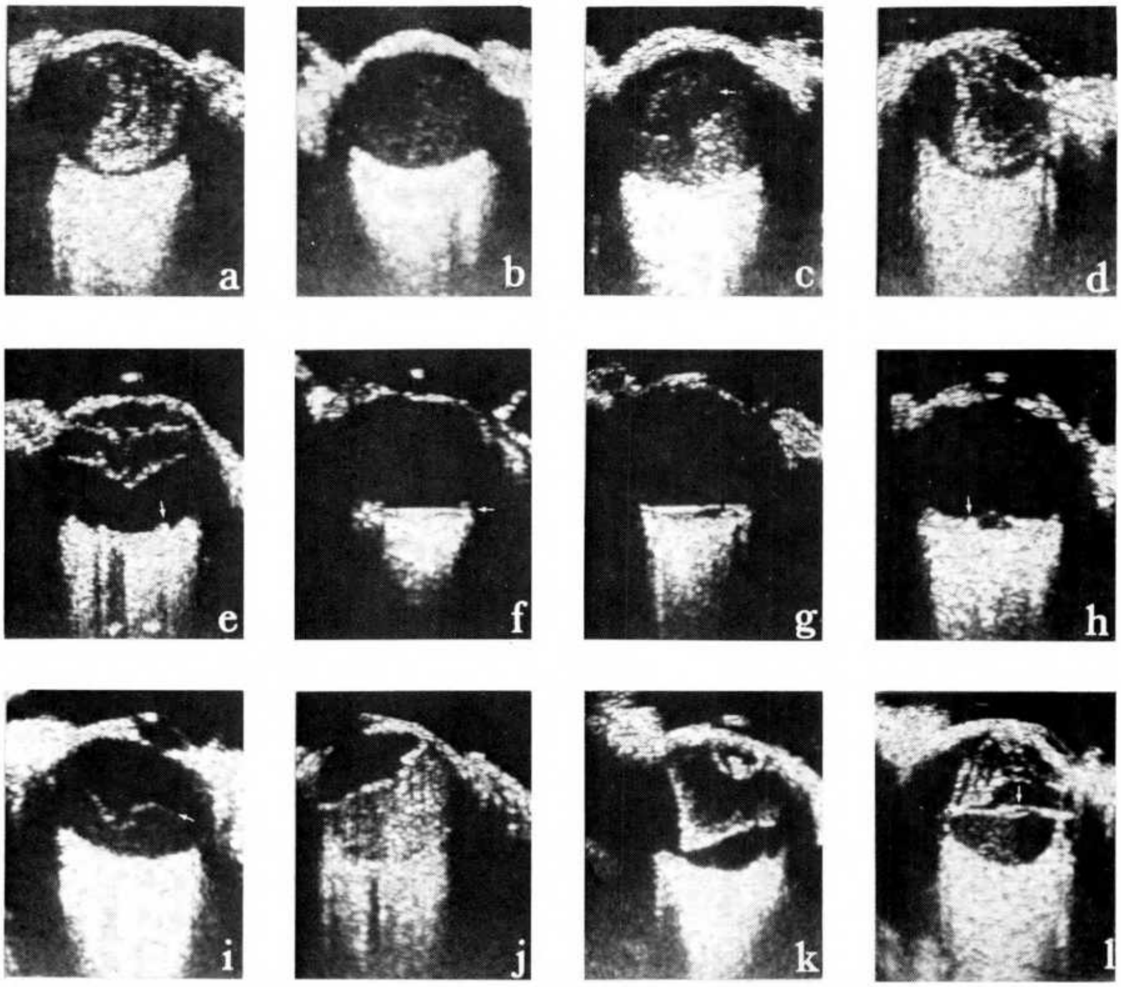

Fig. 1 *Horizontal B-scan sections.* (a) *Haemorrhage in mobile detached gel; clear retrohyaloid space.* (b) *Retrohyaloid haemorrhage; clear gel.* (c) *Retrohyaloid haemorrhage; central gel haemorrhage with clear cortical gel (arrow).* (d) *Eye deviated to right; intragel haemorrhage with some arrangement into membranes.* (e) *Intragel haemorrhage arranged into anterior intragel and posterior hyaloid membranes; clear retrohyaloid space; lens related artefact (Baum's bumps) on posterior retina (arrow).* (f) *'Fluid-level' from sedimentation of blood in fluid vitreous (arrow).* (g) *Eye deviated to right; 'fluid-level' of sedimented blood.* (h) *Thick fibrovascular epiretinal membranes on posterior retina (arrow) excluding the macula.* (i) *Retrohyaloid haemorrhage and mobile posterior hyaloid membrane (arrow); clear gel.* (j) *Eye deviated to left; dense retrohyaloid haemorrhage and posterior hyaloid membrane outlined; clear retracted gel.* (k) *Eye deviated to right; intragel haemorrhage compacting in cortical gel to form 'ochre membrane'; gel tethered to optic disc.* (l) *Eye deviated to right; fibrotic posterior hyaloid membrane (arrow) between vitreous base anteriorly and posterior vitreoretinal adhesion; central intragel and retrohyaloid haemorrhage.*

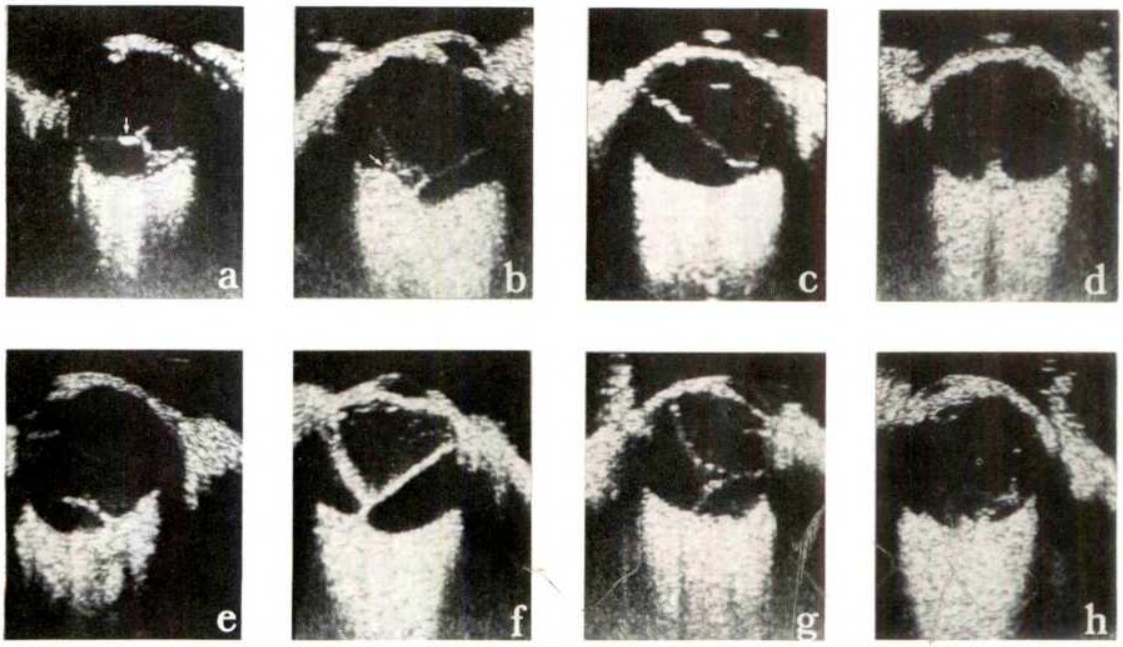

Fig. 2 *Horizontal B-scan sections.* (a) *Eye deviated to left; fibrovascular stalk from optic disc; fibrocellular and fibrovascular* (*arrow*) *components of rigid posterior hyaloid membrane; traction retinal detachment at base of peripapillary stalk.* (b) *Eye deviated to right; posterior hyaloid membrane between vitreous base anteriorly and margins of extensive vitreoretinal adhesion in posterior pole* (*arrow*). (c) *Incomplete posterior vitreous detachment with temporal vitreoretinal adhesion.* (d) *Thick fibrotic stalk from optic disc.* (e) *Rigid prepapillary fibrovascular stalk and retrohyaloid haemorrhage.* (f) *Intragel haemorrhage with arrangement along posterior hyaloid interface; stalk-like vitreoretinal adhesion posteriorly.* (g) *Eye deviated to right; detached gel outlined by haemorrhage, and prepapillary vitreoretinal adhesion.* (h) *Eye deviated to left; 2 posterior vitreoretinal adhesions.*

dynamic studies, the detached gel moving as a corporate body within the fluid retrohyaloid space. Alternatively, or additionally, posterior vitreous detachment was indicated by the presence of echoes from the posterior hyaloid interface. If the gel was mobile and contained opacity, echoes along this interface were considered to arise from blood products in the cortical gel (Figs. 1d, e); a gradual compaction of such intragel echoes within the posterior hyaloid interface was characteristic of 'ochre membrane' formation (Fig. 1k). If a fine sheet of high amplitude echoes arose from the posterior hyaloid interface but the gel boundary was rigid, the posterior hyaloid membrane was considered to be fibrocellular in nature (Fig. 1l). In other cases a thicker sheet of high amplitude echoes arose from the rigid gel boundary, and the posterior hyaloid membrane was considered to be composed of fibrovascular tissue (Fig. 2a). On occasions, several different types of membrane were found in the same eye.

Posterior vitreous detachment could be complete or incomplete. If incomplete, there might only be a single vitreoretinal adhesion (Figs. 2a, b, c), which was often stalk-like (Figs. 2d, e, f, g). Multiple vitreoretinal adhesions were also demonstrable (Fig. 2h), especially by consecutive serial scanning of various levels within the eye.

Detachment of the retina was indicated by membrane-like echoes of high amplitude which tethered at the ora serrata and the optic nerve head when total. Some retinal detachments showed undulating movements on dynamic testing, but movement of the retina was usually restricted or absent. Occasionally a fibrotic posterior hyaloid membrane tethering at the optic nerve head mimicked a total retinal detachment in topography and in echo amplitude (Fig. 3a).

In this series, however, retinal detachment was frequently localised, for example, traction detachment at the base of a vitreoretinal stalk (Figs. 2a and 3b); more extensive detachments were related to wider areas (or multiple areas) of vitreoretinal adhesion (Figs. 3c, d, e, f, g, h). In other eyes an anterior detachment of the retina was noted in the vitreous base region (Figs. 3i, j) with a rigid hyaloid membrane connecting the detached basal retina to posterior sites of vitreoretinal adhesion. In several cases point-like echoes were detected in the subretinal space, particularly when the history suggested a long-standing retinal detachment (Figs. 3k, l).

Discussion

Proliferative retinopathy is one of the most serious sight-threatening complications of diabetic eye disease. New blood vessels, arising as a response to retinal ischaemia, penetrate the inner limiting

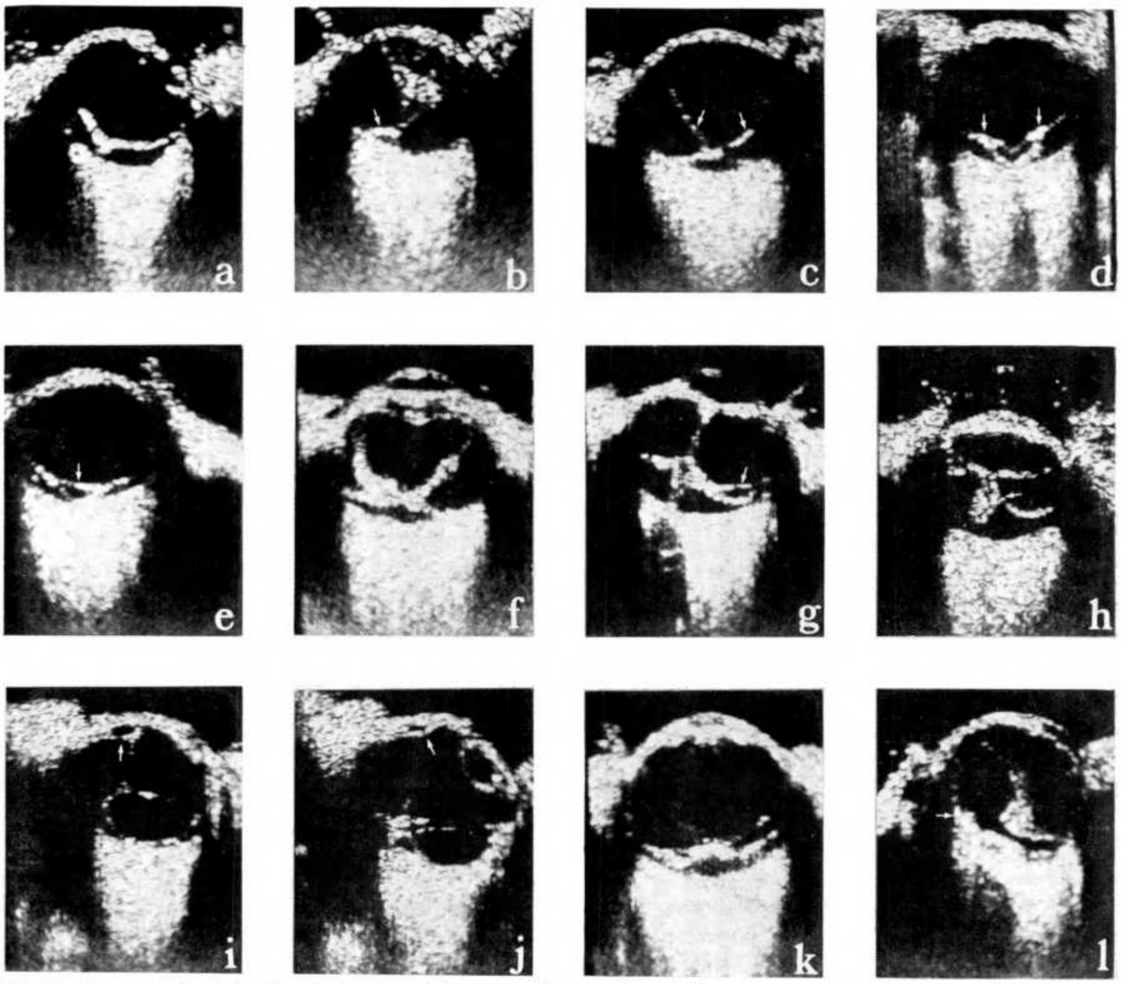

Fig. 3 *B-scan sections.* (a) *Eye deviated to right; gross fibrovascular proliferation tethering at disc.* (b) *Eye deviated to right; haemorrhage in collapsed rigid gel; localised retinal detachment around base of vitreoretinal adhesion* (*arrow*). (c) *Localised detachment of posterior retina; posterior hyaloid membrane* (*arrows*) *inserts into epiretinal fibrous tissue at summit of traction.* (d) *Vertical B-scan section; retinal detachment tethering at optic disc; fibrovascular epiretinal tissue at summit of traction* (*arrows*)*; fibrocellular posterior hyaloid membrane bridging between posterior vitreoretinal adhesions.* (e) *Two localised shallow retinal detachments and 'bridging' posterior hyaloid membrane* (*arrow*). (f) *Extensive fibrotic vitreoretinal adhesion and traction retinal detachment.* (g) *Extensively detached retina tethering at optic disc; widespread vitreoretinal adhesions and rigid posterior hyaloid membrane* (*arrow*). (h) *Grossly detached retina* (*arrow*) *suspended from rigid retracted posterior hyaloid membrane.* (i) *Eye deviated to right; posterior hyaloid membrane and stalk; traction retinal detachment in vitreous base region* (*arrow*). (j) *Eye deviated to right; retinal detachment at vitreous base anteriorly* (*arrow*) *and in posterior pole.* (k) *Extensive fibrotic traction retinal detachment and subretinal echoes.* (l) *Eye deviated to right; haemorrhage in detached gel; clear retrohyaloid space; shallowly detached retina and echoes from subretinal space* (*arrow*).

lamina of the retina and grow within the cortical gel to form vascularised epiretinal membranes. The presence of extensive fibrovascular membranes on the retinal surface may be detected by ultrasound, since the normal smooth concave contour of the posterior globe is disrupted. Nevertheless, care must be taken to differentiate such fibrosis from shallow retinal detachment, a fluid level of dense haemorrhage on the retinal surface, and artefacts produced by the lens (for example, Baum's bumps).

There are 3 important consequences of diabetic epiretinal vasoproliferation: (i) *fibrous contraction* within the epiretinal membrane and consequent tangential traction on the retina; (ii) *an exaggerated adhesion* between the vitreous gel and the retina owing to incarceration of cortical gel in the vascularised epiretinal membrane; (iii) *separation* of the cortical gel from the retinal *except* at these sites of exaggerated adhesion (and also excepting the adhesion at the vitreous base)—'incomplete posterior vitreous detachment'.

During or after vitreous detachment bleeding often occurs into the vitreous cavity owing to traction on new vessels at sites of persistent vitreoretinal adhesion (Davis, 1965; Tolentino *et al.*, 1966). Haemorrhage may be located within the gel, in the retrohyaloid space, or in both compartments, and is the commonest indication for ultrasonic examination in diabetic eye disease. In those eyes in which the detached gel retains its mobility an apparent 'compaction' of blood on the inner aspect of the posterior hyaloid interface can sometimes be observed—'ochre membrane formation'. However, fully formed ochre membranes proved to be relatively infrequent in diabetic vitreous haemorrhage (Table 1).

The detached posterior hyaloid interface often forms a scaffold on which fibrovascular tissue proliferates and extends anteriorly—'forward new vessels' or 'retinitis proliferans'. In addition the more anterior part of the posterior hyaloid interface may also be immobilised by condensation of the cortical gel or proliferation of a non-vascularised fibrocellular membrane connecting the posterior border of the vitreous base to the retinitis proliferans (Lee, 1968). The fibrocellular and fibrovascular components of the posterior hyaloid membrane can often be delineated and differentiated by ultrasound, fibrovascular tissue giving rise to a series of echoes of longer duration than fibrocellular membranes.

In some eyes in this series both mobile and rigid components of the posterior hyaloid interface could be detected. In general, however, echo compaction and ochre membrane formation (characterised by gel mobility) and fibrotic membrane formation (which is characteristically rigid) were mutually exclusive. Fibrovascular invasion (or 'organisation') did not involve the gel itself in our cases; the apparent 'vascular pulsation' detected by A-scan techniques (Ossoinig, 1972) in so-called 'organised' gel probably arose from mobile intragel opacity (McLeod and Restori, 1977).

Contraction of fibrous tissue on the retinal surface (tangential traction) and along the detached posterior hyaloid interface (anteroposterior and bridging traction) may ultimately result in retinal detachment (as in over half of the eyes in this series). Diabetic traction detachment has a characteristic ultrasonic appearance: the retinal elevation is angular in configuration and immobile on dynamic testing; there is associated epiretinal fibrosis at the summit of traction to which the posterior hyaloid membrane is attached; and the retinal surface has an anterior concavity between the limit of detachment and the vitreoretinal adhesion. However, in a majority of extensive diabetic detachments there are associated retinal holes (Tasman, 1972), so the detached retina may have an anterior convexity, and dynamic testing may even reveal a degree of retinal mobility.

Posterior detachment of the vitreous is a crucial stage in the progression of proliferative retinopathy to haemorrhage and retinal detachment (Davis, 1965). In our series vitreous detachment was identified ultrasonically in 95% of eyes. An ultrasonic diagnosis of 'complete posterior vitreous detachment' was made in 10% of these eyes. This was probably an overestimate, since peripheral postbasal vitreoretinal adhesions are often difficult to detect, especially in the presence of retrohyaloid haemorrhage. Nevertheless in some elderly patients a highly mobile gel was identified in the anterior part of the vitreous cavity—the typical ultrasonic pattern of 'posterior vitreous detachment with collapse'.

The more usual *incomplete* posterior vitreous detachment of proliferative retinopathy results from variable numbers and sites of persistent vitreoretinal adhesion (Foos, 1972). Such adhesions usually indicate, by inference, the extent of epiretinal fibrovascular proliferation present at the time of vitreous detachment. In some eyes neovascularisation is very limited in extent, the detached gel being tethered posteriorly only by a single adhesion to the optic nerve head. Retinal detachment is not generally seen in such cases, except occasionally round the base of the prepapillary stalk. In many eyes, however, fibrovascular proliferation on the surface of the retina is extensive by the time of posterior vitreous detachment: this results in multiple or widespread sites of persistent vitreoretinal adhesion. It is in these eyes that associated retinal detachment is generally observed, and crucial clinical decisions on vitreous surgery often depend on the ultrasonic diagnosis of retinal detachment, especially if the macular retina is involved. However, those eyes with extreme degrees of fibrotic rigidity of the retina or dense subretinal opacity are generally deemed inoperable.

We thank Miss Penny Davies for typing the manuscript.

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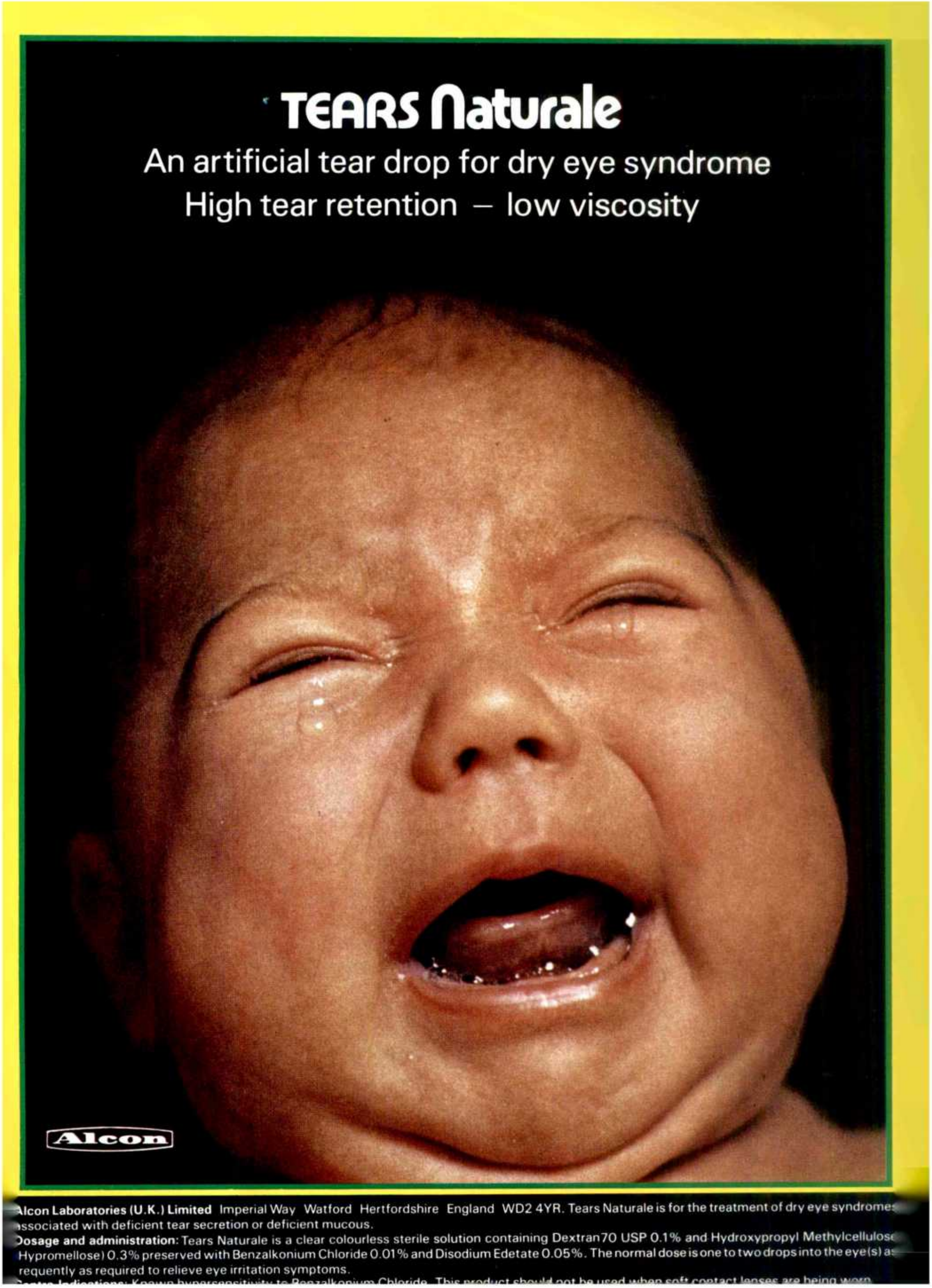

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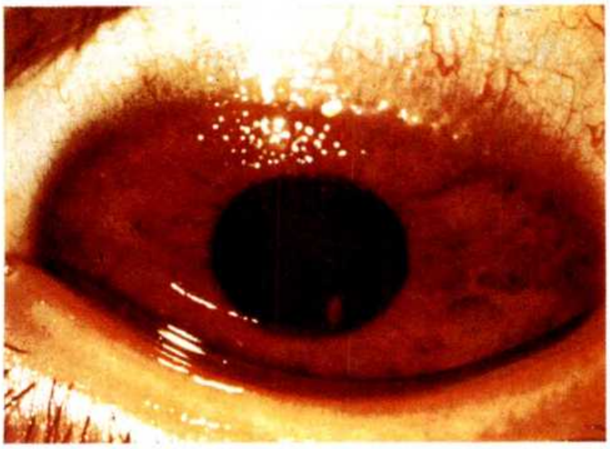
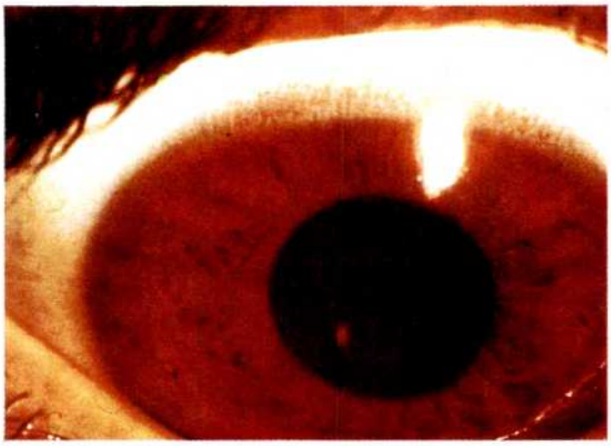


a. The superior limbus in a placebo treated eye of a patient suffering from vernal kerato-conjunctivitis, stained with fluorescein. Note the limbal hyperaemia and swelling and the irregularity of the corneal surface.



b. The opposite eye of the same patient treated with sodium cromoglycate eye drops. Before treatment, both eyes appeared similar.

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Allergic diseases of the eye may have extremel distressing symptoms. In the worst cases, itching, soreness, photophobia or blepharospasm can cause such severe discomfort that otherwise strong and healthy patients may become severely incapacitated.

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Dark adaptation in diabetes mellitus

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SUMMARY The effect of diabetes mellitus on the normal dark adaptation curve is investigated. It has been found that diabetic patients take longer to adapt and that their absolute thresholds are raised. The degree of elevation in the final threshold correlates with the duration of diabetes.

Many systemic conditions are known to have side effects that affect vision. One of these is diabetes mellitus. Besides the rapid fluctuations in refraction that frequently occur during the initial stages of this condition, which are related to fluctuations in the blood glucose level, the majority of visual effects are related to the frequently encountered retinopathy. While considerable research has been undertaken towards understanding the retinal changes that occur in this retinopathy, relatively little research has been directed towards documenting the type of visual loss that is concurrent with it, Roth (1969) and Bloom *et al.* (1972) being notable exceptions.

In this paper we report on the effects of diabetes mellitus on the normal dark adaptation curve. While it has previously been mentioned (François *et al.*, 1978) that light thresholds are often raised in diabetes, we have been unable to find any report on the quantitative measure of this effect.

Materials and methods

Measurements of the dark adaptation curve were taken with an H-A Dark Adaptometer (Henson and Allen, 1977). This adaptometer measures the time taken for subjects to be able to see each of 12 discrete levels of gradually decreasing intensity. The adaptometer is initially set at its brightest intensity level of 16·6 cd/m^2. Once the subject has reported that he can see this, the intensity is reduced to the next lowest discrete level, the subject again being asked to report as soon as he can see the light. The experimenter records the time taken for each of the intensity levels to be seen. To assist the subject in being able to recognise when they can see the light it is made to flash at approximately 0·5 Hz.

The dark adaptation measurements were taken monocularly on the right eye with the exception of 2 subjects in whom the vision in that eye was so poor that reliable results could only be obtained with the left eye. Subjects were preadapted for 1 minute by seating them with their faces against a large opal screen whose intensity was $17{\cdot}4\times10^2$ cd/m^2. At the end of this period the adapting light was turned off and the subject's attention directed towards the adaptometer. The test continued until the subject had seen all the intensity levels or until he had been in the dark for a total of 1400 s (23 min 20 s).

Fixation was controlled during adaptation by asking the subject to direct his attention towards a small dim red light attached to the adaptometer which positioned the flashing patch 20 degrees from the fovea. The patch itself subtended 12 degrees at the eye.

After measurement of the dark adaptation curve the subject's visual acuities were recorded. If they were below 6/9 a retinoscopic refraction was performed to establish whether the lowered VA was a result of a refractive error. The subject's pupil was then dilated and a careful direct ophthalmoscopy performed. The results from this were supported by a fundus photograph taken with a Kowa camera.

Details about the duration of diabetes, age of the subject, and type of medication were also recorded.

Subjects were asked specifically if they had any visual problems and if they had noticed any increased difficulty either in seeing in the dark or in getting used to the dark.

Results

A total of 35 diabetics were tested. Their ages ranged from 11 to 73 years and their duration of diabetes from 3 months to 51 years. Six of the subjects were excluded from the analysis of the data because they had visual problems other than those

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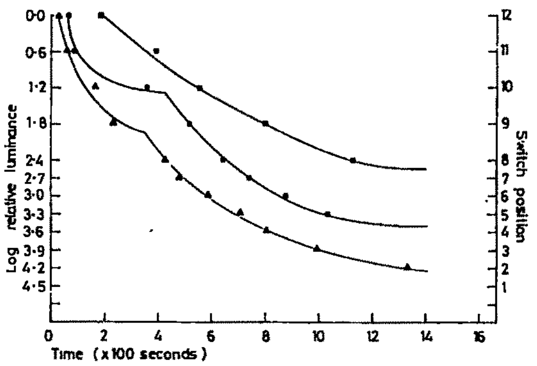

Fig. 1 *Typical dark adaptation curves.* ▲ *Case 1.* ● *Case 2.* ■ *Case 3*

commonly encountered in diabetes. Three of them suffered from high blood pressure with related retinal changes, 2 had cataracts, and the final 1 had macular degeneration.

Typical dark adaptation curves for 3 of the subjects are shown in Fig. 1. The first of these, case 1, is essentially normal in both its time course and its final threshold. The second curve, case 2, shows an elevation in the final threshold of a little over 0·6 log units and an increase in the time taken to see each of the stimuli. The third curve, case 3, is grossly abnormal, showing both a marked rise in final threshold and a much delayed response.

From the ophthalmoscopic findings subjects were divided into 4 groups: (1) Those showing no fundus abnormalities. (2) Those showing only 1 or 2 dot haemorrhages. (3) Those showing several clusters of haemorrhages and exudates. (4) Those showing fairly extensive bleeding and exudates. Groups 2, 3, and 4 all fell within the intraretinal catagory of diabetic retinopathy as described by Cogan (1974).

The final thresholds reached by the 29 subjects are shown, plotted against the age of the subject, in Fig. 2. (The final threshold for each subject was taken as the intensity of the patch at the last switch position which was seen prior to the end of the test.) The bold line on this graph shows the normal rise in threshold known to occur with age. This line has been computed from the data of McFarland and Fisher (1955), which show a rise in threshold of 0·003 log units/year. The starting point for this line has been obtained from a series of 10 normal subjects all between the ages of 20 and 22 who were tested with this adaptometer prior to the present study.

It can be seen from Fig. 2 that a good number of the subjects had final thresholds considerably above the mean for their age group. However, the scatter of the results is so large that no general trend between threshold elevation and age can be seen. The data have been replotted in Fig. 3 as the degree of elevation above norm for their age versus the duration of diabetes. By plotting the data in this way the degree of scatter has been substantially reduced. The line drawn on this graph is the least squares fit of the degree of elevation on the duration of diabetes. It can be seen from this diagram that all 3 subjects who had had diabetes for more than

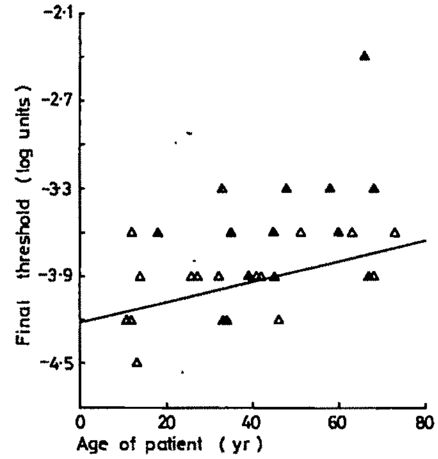

Fig. 2 *Final threshold reached after 1400 s in the dark versus the age of the patient. The solid line represents the normal increase in threshold seen with age. The symbol* △ *is for subjects with no retinal changes,* ▲ *for subjects with 1 or 2 dot haemorrhages,* ▲ *for subjects with several clusters of haemorrhages and some exudates,* ▲ *for subjects showing fairly extensive haemorrhages and exudates*

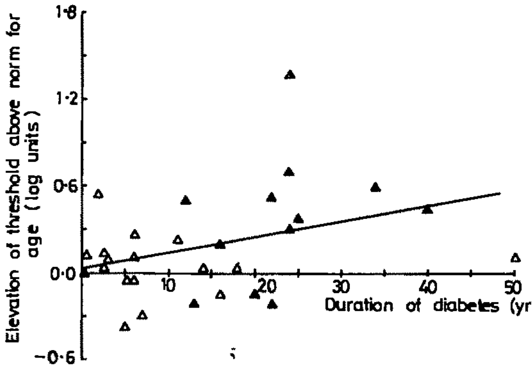

Fig. 3 *The elevation in final threshold above the norm for their age versus the duration of diabetes. The solid line is the least squares fit to the data. The meaning of the symbols* △, ▲, ▲, *and* ▲ *is the same as that in Fig. 2*

22 years had raised dark adaptation thresholds above the norm for their age.

The mean rise in final threshold of the 6 subjects not included in the data analysed was on average above that of the remaining 29 subjects.

Discussion

The data indicate that a large number of diabetics have final thresholds above the norm for their age. The amount of elevation is roughly correlated ($r=0{\cdot}534$) with the duration of diabetes. There is, however, considerable spread in the data, some subjects showing considerable elevation after only a few years of diabetes while others who have had the condition for many years show no significant elevation.

The percentage of subjects above the norm for their age is approximately the same for those with and without retinal changes, though the former had on average a much larger increase in their final thresholds.

Cogan (1974) has shown that the retinal changes associated with diabetes often produce ischaemic areas with little, if any, capillary network. These areas could be expected to have a much larger loss in sensitivity than those in which the capillary network is still intact. If in the process of measuring dark adaptation the stimulus were to fall on one of these ischaemic areas, the elevation in final threshold would be expected to be greater than if it fell on some other area. This factor alone could account for a fairly large amount of variability in response seen in subjects with identical degrees of retinopathy as detected with the ophthalmoscope.

McFarland *et al.* (1946) have shown in normal persons that the differential threshold is increased during periods of hypoglycaemia and that the degree of elevation is maximal at the lower intensity levels. Thresholds measured on diabetics may fluctuate in an analogous manner according to the blood sugar level at the time of testing, creating even more variability in the responses.

The results showed that there was no correlation between the threshold elevation and the visual acuity of the subjects. All of them with the exception of 2 had corrected acuities of 6/9 or better in the tested eye. The 2 remaining had acuities of 6/12 and 6/18. The subject with the 6/12 acuity had a 1 degree convergent strabismus and the subject with the 6/18 acuity had one of the more advanced retinopathies.

Only 2 of the subjects of the 35 tested reported any increased difficulty in seeing at night or in getting used to the dark. Both of these subjects had retinal or media changes other than those commonly found in diabetics, that is, they fell within the group of 6 subjects excluded from the analysis of the data. This failure to report any increased difficulty was despite the fact that 20% of them showed marked elevations in final thresholds (greater than 0·5 log units) and 20% took more than 3 times the normal time to see switch position number 10 (intensity 1·05 cd/m^2). (Statistical analysis showed a correlation ($r=0{\cdot}739$ between the final threshold and time taken to reach switch position number 10.) The average time for normal persons, taken from the beginning of the test (when the preadapting light had been turned off), to see this intensity was 100 s.

The fact that our subjects did not experience any increased difficulty in seeing in the dark is not surprising, since they would rarely have to perform any visual tasks at intensities anywhere near the lowest levels tested in this experiment. What is surprising is that they did not report any increased difficulty in getting used to the dark. Switch position number 10 was specifically chosen for analysis because the intensity of the light at that position falls above the alpha point in normal subjects and is in the range of intensities frequently encountered at night in the urban visual environment.

The driving performance of diabetics must thus be of considerable concern to their physicians. While many diabetics may be within normal limits, there is a substantial deficit in the visual ability of some diabetics to drive safely at night. Their recovery from glare from oncoming headlights must be considerably above the norm. This disability will not be detected by either ophthalmoscopy or measurement of visual acuity.

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British Journal of Ophthalmology, 1979, 63, 542–546

Blepharochalasis

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SUMMARY The condition of blepharochalasis and its treatment are discussed. Four cases are presented which show a physical sign that may help in its diagnosis.

Blepharochalasis is a relatively rare but distinctive condition characterised by recurrent attacks of eyelid oedema which often result in an acquired ptosis. It was first described by Beer (1817) and later given its name by Fuchs (1896). Since that time there have been many reports of the clinical and pathological findings. After recurrent and unpredictable attacks of oedema the eyelid skin becomes wrinkled, redundant, discoloured, thinned, and laced by tortuous vessels. Fuchs (1896) described the skin as having a cigarette-paper appearance.

Blepharochalasis is usually bilateral but may be unilateral. Two stages of the condition have been described. In the early stage the skin and eyelid tissues may become hypertrophied with oedema which does not pit on pressure (Benedict, 1926). This is followed by a thinning and atrophy of the skin and all the eyelid tissues, giving the characteristic skin appearance and ptosis. Most cases present in the atrophic state, and it is not certain whether they have ever passed through a so-called hypertrophic stage. Fine skin nodules have been described (Verhoeff and Friedenwald, 1922), but may be only a secondary association with previous surgery. Herniation of fat through a weakened orbital septum occurs (Schmidt-Rimpler, 1899). The lower lids may also be affected (Stein, 1930), and the generalised laxity of the tissues may lead to blepharophimosis (Friedenwald, 1923).

The various pathological findings have been summarised by Alvis (1935). The main changes are in the blood vessels, which are dilated and increased in number. These are associated with a proliferation of the endothelium of the capillaries and venules. There is a loss of elastic tissue and a generalised infiltration of the tissues with round cells. The epithelium is thinned and atrophic, with vacuolation of the basal cells. The aetiology of these changes remains unknown.

The attacks of oedema usually begin around puberty, which might suggest an endocrine imbalance. They resemble attacks of angioneurotic oedema of the eyelids (Fuchs, 1896), which might be due to an allergic diathesis. Patients with angioneurotic oedema may subsequently develop the characteristic skin changes of blepharochalasis (Verhoeff and Friedenwald, 1922), but no deficiency of C'1-esterase inhibitor was found in a patient with blepharochalasis (Beard, 1976). Ascher (1922) described the triad of blepharochalasis, swelling of the mucous membrane of the lips, and nontoxic thyroid enlargement, suggesting that it could be part of a more generalised disorder. Most cases of blepharochalasis, however, are limited to the eyelids, and no generalised abnormality has been described.

Treatment is surgical. Redundant skin should be excised. A prolapsed lacrimal gland can be sutured back into position. A minimal ptosis may be successfully treated with a Fasanella-Servat (1961) procedure. Greater degrees of ptosis require more major surgery, but this may easily result in an overcorrection if the condition is not properly diagnosed. Recurrent attacks of eyelid oedema can ruin a previously good postoperative result. The timing of surgery is therefore difficult. Since the frequency of attacks decreases with age, it would seem reasonable to wait until the disease is quiescent before attempting surgery (Stieglitz and Crawford, 1974).

This is a report of 4 cases of blepharochalasis which show a previously poorly described feature of the condition. The results of surgical correction are presented and the cause of the ptosis is discussed.

Patients

CASE 1

A man aged 31 presented with a bilateral acquired ptosis following recurrent attacks of eyelid oedema. The attacks had started about 13 years previously and there had been about 15 attacks in all lasting between 24 hours and 3 days. He had a history of

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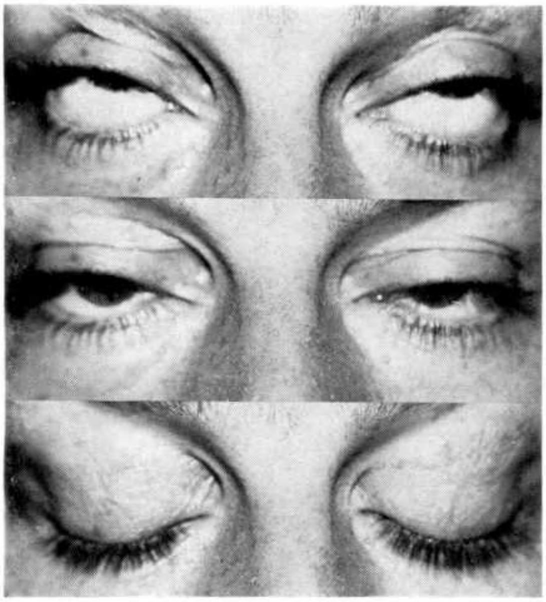

Fig. 1 *Case 1: preoperatively showing bilateral ptosis with good levator function and atrophy of the nasal fat pads, more marked on the right, producing pseudo-epicanthic folds*

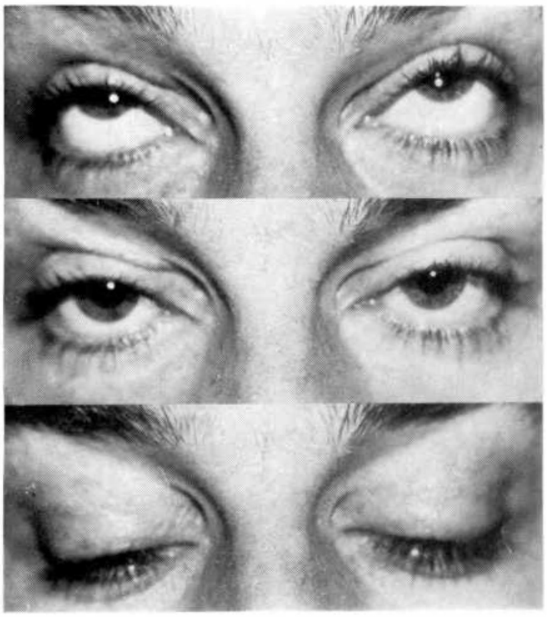

Fig. 2 *Case 1: Postoperatively*

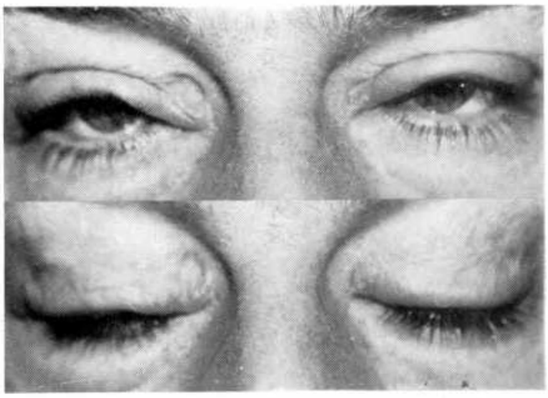

Fig. 3 *Case 1: Postoperative attack of eyelid oedema in primary position and on down-gaze*

possible allergy to aspirin but did not suffer from asthma, eczema, or hay fever. There was no family history of any similar condition or of other allergies.

On examination he had a marked bilateral ptosis with the typical thin wrinkled skin and considerable atrophy of the nasal fat pad, giving the appearance of a pesudoepicanthic fold on both sides. The vertical palpebral apertures were 7 mm on the right and 6 mm on the left, and the levator function was good, being 10 mm on the right and 11 mm on the left (Fig. 1). The unaided visual acuity was 6/6 on the right and 6/60 on the left. This left amblyopia was associated with a left convergent squint. No other ocular abnormality was detected. A Tensilon test was negative.

Bilateral upper lid surgery was performed by an anterior approach. The aponeurosis was not disinserted but was thinned. It was tucked and excess skin was excised. Postoperatively he was much improved. The palpebral apertures were 8·5 mm on both sides and the levator function was 15 mm (Fig. 2). He continued to have intermittent attacks of eyelid oedema (Fig. 3), which accentuated the atrophy of the nasal fat pads. The duration of these attacks was not influenced by systemic prednisolone 5 mg 4 times a day and cold compresses. Five years later the ptosis is recurring, and further surgery is being considered.

CASE 2

A boy aged 15 presented with a right ptosis which had progressed over the previous 3 years. It was now stable although appeared worse when he was tired. He got recurrent attacks of swelling of the right eyelid, especially when he had a cold, but there was no history of any allergies and no significant family history.

On examination he had 2 mm of right ptosis with good levator function (Fig. 4). The palpebral apertures were 7 mm on the right and 9 mm on the left, and the levator function was right 13 mm and

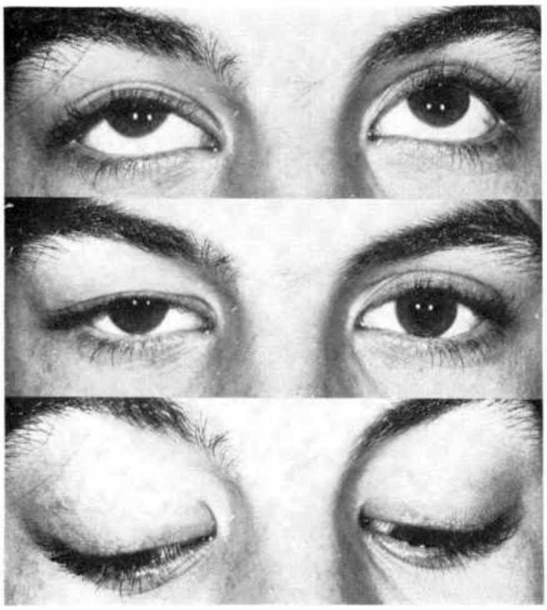

Fig. 4 *Case 2: Preoperatively showing 2 mm of right ptosis with good levator function*

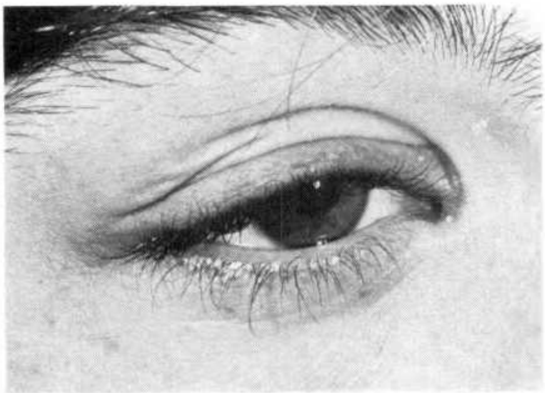

Fig. 5 *Case 2: Right eye showing redundant skin and atrophy of the nasal fat pad producing a pseudoepicanthic fold*

left 15 mm. The right eyelid remained lower than the left in all positions of gaze, suggesting an acquired type of ptosis. The skin of the upper lid was redundant and thinner than on the left, with visible blood vessels, and he had a marked atrophy of the nasal fat pad, producing a pseudoepicanthic fold on that side (Fig. 5). The unaided visual acuity was 6/9 in the right eye and 6/6 in the left eye. There were no other ocular or general physical abnormalities.

Ptosis surgery was performed via an anterior skin approach. The aponeurosis was found to be extremely thin and stretched; 6 mm of this tissue were resected and healthy looking aponeurosis was sutured to the anterior tarsal surface 3 mm from the upper tarsal border (Fig. 6). Excess skin was excised and the skin crease reformed with interrupted sutures which picked up the underlying aponeurosis. Postoperatively the result was satisfactory (Fig. 7).

CASE 3

A girl aged 13 presented with a bilateral ptosis and a history of recurrent attacks of eyelid oedema since the age of 7. She had undergone a left ptosis correction 1 year previously, but the ptosis had recurred. There was no history of any allergy and no significant family history.

On examination she had a bilateral acquired ptosis worse on the left. The left palpebral aperture was 4 mm and the right 5 mm. The levator function was good, being 12 mm on the right and 10 mm on the left. The eyelid skin was markedly thin and atrophic. There was a marked atrophy of the nasal fat pad on both sides, giving her pseudoepicanthic

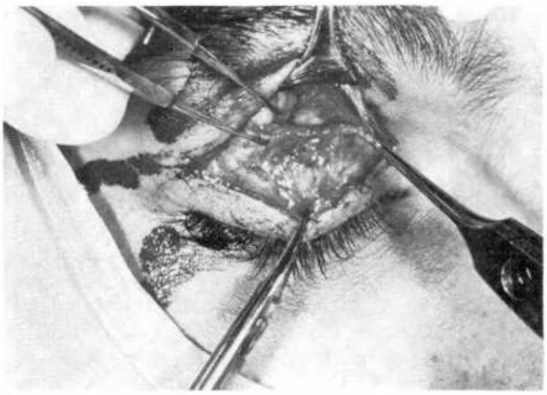

Fig. 6 *Case 2: Operative picture showing aponeurosis held in forceps. This was sutured to the anterior tarsus just above the point of the scissors*

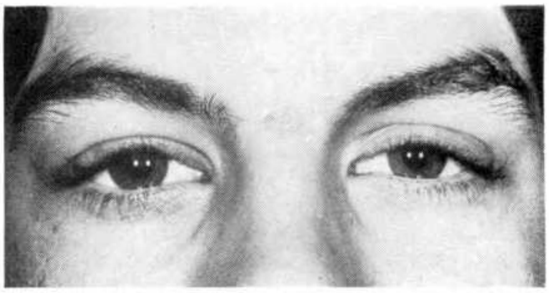

Fig. 7 *Case 2: In primary position postoperatively*

folds, and she had multiple small nodules in the skin of the left upper eyelid (Fig. 8). The unaided visual acuity in the right eye was 6/6 and in the left 6/9. There were no other ocular or physical abnormalities.

Bilateral ptosis surgery via an anterior approach was performed. Excess skin and the thinned aponeurosis were excised and healthy aponeurosis sutured to the tarsal plate. The postoperative appearance was much improved, but a subsequent attack of oedema led to a recurrence of the left ptosis, especially nasally (Fig. 9).

CASE 4

A man aged 25 presented with a left acquired ptosis following recurrent attacks of left upper eyelid oedema.

On examination he had about 3 mm of left ptosis with good levator function. The lid skin showed the typical thin, wrinkled appearance with the characteristic fat atrophy and pseudoepicanthic fold (Fig. 10, upper). At ptosis surgery by the conjunctival approach the thinned aponeurosis and a small amount of the levator muscle itself were resected. This led to an initial overcorrection (Fig. 10, middle) which was satisfactorily corrected by the early removal of sutures and massage (Fig. 10, lower).

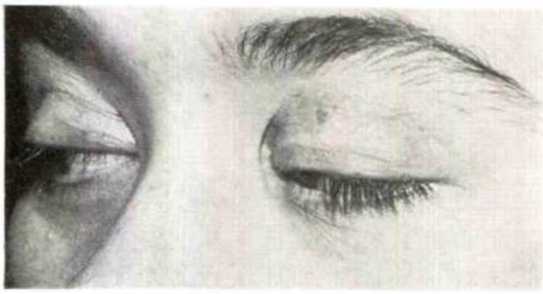

Fig. 8 *Case 3: Showing atrophy of nasal fat pad producing a pseudoepicanthic fold. The left eyelid skin has multiple small skin nodules*

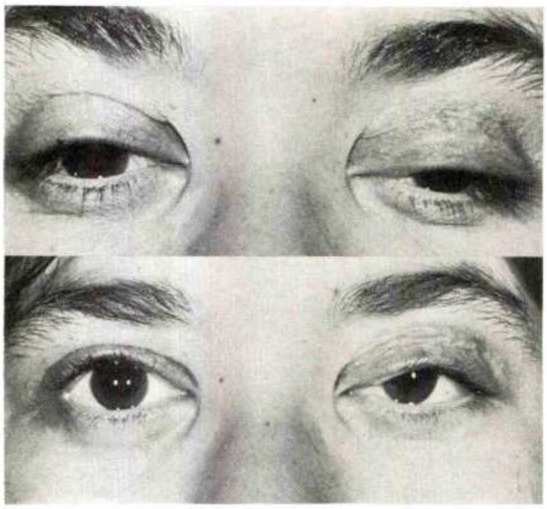

Fig. 9 *Case 3: Pre- and postoperative appearance. A postoperative attack of oedema led to a recurrence of the ptosis nasally in the left eye*

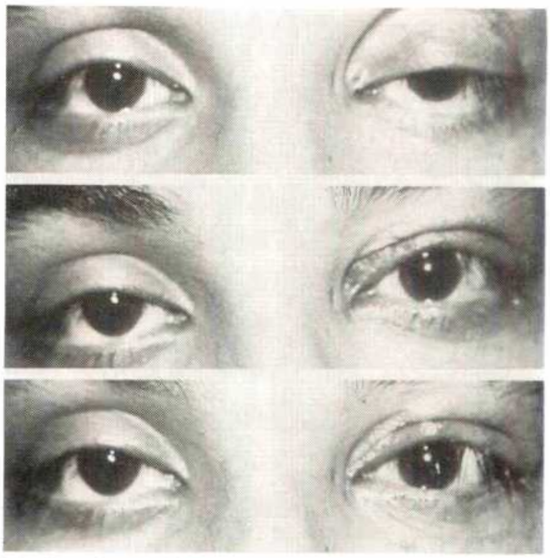

Fig. 10 *Case 4: Upper: Preoperative appearance showing left ptosis. Middle: Immediate postoperative appearance showing overcorrection. Lower: Late postoperative appearance after suture removal and massage*

Discussion

These 4 cases illustrate many of the accepted features of the condition. There is always a history of recurrent attacks of eyelid oedema leading to the characteristic skin appearance. In addition fine skin nodules may be present if the patient has undergone previous surgery (Case 3). The attacks usually start around puberty. In our youngest patient they began at the age of 7 (Case 3) and were still continuing in our oldest at the age of 35 (Case 1). The condition may be unilateral (Cases 2 and 4) or bilateral (Cases 1 and 3), and affects both sexes. Only 1 previous report (Alvis, 1935) has described the very distinctive atrophy of the nasal fat pad and the pseudoepicanthic fold which all our cases show. Why the medial fat pad should atrophy so markedly is not clear, but a review of published photographs of previously described cases shows that this is a very common feature of the condition.

The ptosis is acquired and the more affected eyelid is lower than on the less or unaffected side on both up-gase and down-gaze (Fig. 4). The levator function is good. These factors suggest that the levator muscle itself is not dystrophic. The likely site of the lesion is therefore in the aponeurosis or its insertion, and this was supported by our findings at operation. Jones *et al.* (1975) described ptosis due to a disinsertion of the aponeurosis and its surgical repair. Their operation is very similar to that described by Kreiker (1929) for the repair of the ptosis associated with blepharochalasis.

It seems likely that in blapharochalasis recurrent attacks of eyelid oedema lead to a stretching or disinsertion of the aponeurosis. The aim of ptosis surgery should therefore be to repair this aponeurotic defect. If the levator muscle itself is resected, this will easily result in an overcorrection, as in Case 4. Since the attacks of oedema may continue postoperatively (Fig. 3), surgery should be delayed until they are as infrequent as possible. If recurrent attacks of oedema cause a recurrence of the ptosis, the aponeurotic defect can be repaired again.

Conclusion

Four cases of blepharochalasis are presented. These all show a marked atrophy of the nasal fat pad of the upper eyelid, which gives rise to a deep hollow nasally and a pseudoepicanthic fold. This characteristic is important, since the diagnosis of blepharochalasis must be made on the history and examination. Recognition of this sign may alert the surgeon to make the proper diagnosis and so avoid unnecessary investigations and inappropriate surgery.

Although the aetiology of the condition is unknown, the cause of the ptosis is probably a stretching or disinsertion of the aponeurosis of the levator palpebrae superioris muscle. If this defect is repaired, there is little risk of an overcorrection, and the repair can be repeated if recurrent attacks of oedema lead to a recurrence of the ptosis.

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Dark adaptation testing in heterozygotes of Usher's syndrome

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SUMMARY Fourteen heterozygous carriers of Usher's syndrome were evaluated by ophthalmoscopy and dark adaptation testing. The normal findings in our study are discussed and compared with those of previous reports, which suggested that abnormal dark adaptation thresholds and fundus abnormalities may be seen in heterozygotes.

Usher's syndrome is an autosomal recessively inherited trait that is characterised by a congenital neurosensory hearing defect of varying severity associated with retinitis pigmentosa. The syndrome has been estimated to account for 3% to 6% of congenital deafness and 50% of deaf-blindness (Vernon, 1969). The incidence of the disease is approximately 3 per 100 000 people, and the incidence of carriers is approximately 1 in 100 of the general population (Vernon, 1969).

Previous reports from the ophthalmic literature have noted that heterozygous carriers of Usher's syndrome may show raised dark adaptation final thresholds (De Haas *et al.*, 1970). In some carriers the increase is associated with fundus changes characteristic of gyrate atrophy of the choroid and retina (Holland *et al.*, 1972). Because of the importance of identifying heterozygotes, we examined 14 Usher's syndrome carriers to confirm the presence of either dark adaptation abnormalities or fundus abnormalities, particularly those suggestive of gyrate atrophy of the choroid and retina.

Subjects and methods

All subjects were the natural parents of at least 1 child with a congenital neurosensory hearing defect and retinitis pigmentosa. Affected offspring showed characteristic fundus abnormalities including bone spicule pigmentation, waxy disc atrophy, and attenuated retinal vessels. Additionally, all affected offspring complained of night blindness and showed constricted peripheral fields.

Each heterozygote was questioned about ocular, auditory, and neurological as well as general medical complaints. All had a complete ophthalmological assessment that included the determination of best corrected visual acuity; slit-lamp examination of the anterior segment, lens, and vitreous; and dilated fundus examination by both direct and indirect ophthalmoscopy.

After maximal pupillary dilatation the heterozygous parents had monocular dark adaptation testing by a Goldmann-Weekers dark adaptometer. All were similarly tested by a protocol that began with an initial 5 minutes of adaptation to a white light of 1600 lux. After bleaching, dark adaptation thresholds were measured during a 30-minute period for 2 separate circular 2° test targets obtained by an orange, short-wavelength, cut-off filter (Corning 3482) having 90% transmission at 590 nm and 50% transmission at 555 nm and a blue band-pass filter (Corning 4305) having a transmission peak at approximately 460 nm and 50% transmission at 360 and 540 nm. Each of the chromatic stimuli was presented alternately in an on-off fashion at the rate of 1 second on and 1 second off. The measurements were recorded on a standard log luminance versus time graph. Fixation was maintained with a movable, dimly lit, red fixation light while measurements were made at a retinal locus 15° above the fovea. At each test time 2 on (or ascending) and 2 off (or descending) thresholds were determined. An ascending threshold was the intensity at which the subject first saw the test light as its luminance was increased. The descending threshold was the intensity at which the subject ceased to see the test light as its luminance was lowered. The approximate true absolute threshold was calculated as the average of the 2 ascending

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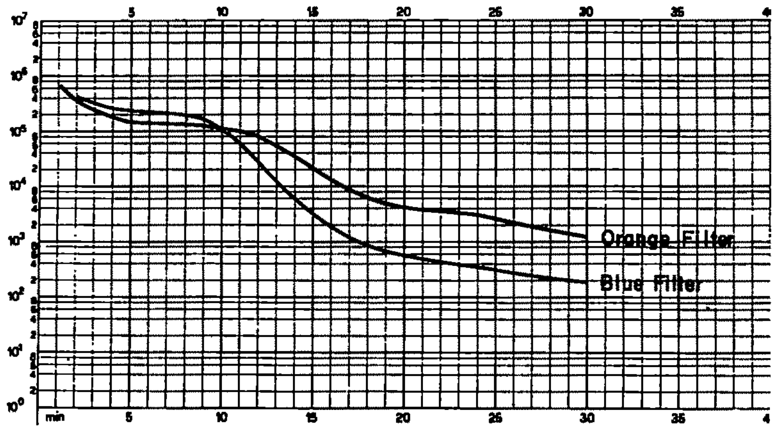

Fig. 1 *Dark adaptation curve from normal subject with blue and orange filters*

and descending thresholds obtained during a test time. Reliability was ascertained by noting the consistency of threshold responses for each subject within each test period. At the 15° locus both cone and rod thresholds and cone-rod break times were obtained. After 30 minutes of testing in the dark, rod thresholds were also measured at 30° and 45° superior and 15°, 30°, and 45° inferior to the fovea by setting the calibrated red fixation target to the appropriate retinal locus.

A technique using alternate orange and blue filter test targets, similar to those described by Zeavin and Wald (1956), provides a way for distinguishing cone and rod thresholds and for measuring cone-rod break times on dark adaptation testing. During initial stages of dark adaptation, when cone receptors determine visual thresholds, the orange threshold lies about 0·15 log units below the blue; whereas later, when rod receptors determine thresholds, the blue threshold lies about 0·95 log units below the orange. Cone-rod break times are determined from the point at which the curves for the orange and blue filters cross (Fig. 1).

Results

The visual acuity and ophthalmological examination findings for all 14 heterozygous carriers of Usher's syndrome were normal. None was observed to have gyrate atrophy of the choroid and retina, and there were no complaints of nyctalopia. On dark adaptation testing, cone and rod thresholds were within the normal range at all retinal loci tested. Tables 1 and 2 compare results at 15° superior to the fovea for normal and heterozygous carriers. Final rod thresholds at 30° and 45° superior to the fovea and at 15°, 30°, and 45° inferior to the fovea were within ±0·5 log units of the values obtained at 15° superior to the fovea for normal controls and

Table 1 *Dark adaptation recordings for 13 normal eyes*

Age (yr)	*Sex*	*Cone threshold (log units*	*Rod threshold (log units)*	*Cone-rod breaktime (min)*
27	F	2×10^4	2×10^2	12·0
54	M	2×10^4	4×10^2	12·5
56	F	6×10^4	3×10^2	10·0
67	M	3×10^4	4×10^2	10·0
25	M	6×10^4	1×10^2	9·0
55	F	1×10^5	2×10^2	8·5
40	F	1×10^5	2×10^2	10·0
38	F	4×10^4	2×10^2	10·0
25	M	4×10^4	1×10^2	8·0
24	F	3×10^4	6×10^2	10·0
32	M	3×10^4	2×10^2	9·0
45	M	3×10^4	3×10^2	9·0
56	F	4×10^4	2×10^2	12·5

Table 2 *Dark adaptation recordings for 14 heterozygotes results were obtained on one eye*

Age (yr)	*Sex*	*Cone threshold (log units)*	*Rod threshold (log units)*	*Cone-rod break time (min)*
35	F	6×10^4	2×10^2	8·0
52	F	1×10^5	3×10^2	8·5
54	M	1×10^5	3×10^2	9·0
51	F	2×10^4	1×10^2	9·0
49	F	4×10^4	2×10^2	9·0
50	M	4×10^4	2×10^2	9·0
45	F	2×10^4	5×10^2	10·5
38	M	6×10^4	6×10^2	12·0
54	M	1×10^5	3×10^2	9·0
67	M	6×10^4	3×10^2	13·5
68	F	3×10^4	4×10^2	11·5
52	F	2×10^4	3×10^2	13·0
47	F	6×10^4	2×10^2	11·5
67	M	4×10^4	4×10^2	13·0

heterozygotes. All 14 heterozygotes showed a normal cone-rod break time measured 15° superior to the fovea.

Discussion

In patients with Usher's syndrome elevated rod thresholds on dark adaptation testing are found even in initial stages of the disease. Eventually cone thresholds are also elevated. In our study of 14 subjects heterozygous for Usher's syndrome no abnormalities were seen on careful ophthalmological examination. Final cone and rod thresholds on dark adaptation examination were found to be within a normal range at 6 loci on the retina by separate 2° orange and blue targets.

Our data do not support previous findings of raised rod dark adaptation thresholds ranging from 1 to 2 log units above normal in 5 of 13 heterozygous carriers of Usher's syndrome (De Haas *et al.*, 1970). Even 'minor degrees of impairment' in 3 additional carriers noted by the same authors were not seen in the present study. In addition, fundus changes showing phenotypic similarities to those noted in gyrate atrophy of the choroid and retina, as reported by Holland *et al.* (1972) in 2 definite and 1 possible heterozygous carriers, were not seen in our 14 subjects.

The 13 heterozygotes reported by De Haas and co-workers were from 3 separate families. The two heterozygotes from family A, aged 61 (VI-2) and 14 years (VIII-1), were the mother and daughter of a patient with congenital deafness and retinitis pigmentosa. They were found to have elevated rod final thresholds of 0·5 and 1·5 log units, respectively. Both complained of nyctalopia and showed abnormal electro-oculogram light/peak to dark/trough ratios. The 61-year-old subject showed fundus changes of choroidal atrophy and a few 'spidery pigment spots'. The fundus of the 14-year-old subject was normal.

Seven of 8 other siblings of the affected patient also had a pigmentary retinopathy. Their disease was characterised by a paucity of bone corpuscular pigmentation, slight pallor of the optic disc, and narrowing of retinal arteries. Further, 4 of the affected members in their fourth decade showed normal central acuity. While all affected patients showed raised rod final thresholds on dark-adaptation testing, in 1 instance the rod final threshold was only slightly raised, while other patients showed final thresholds ranging from 1 to 2·5 log units above normal. The preservation of normal central acuity in at least some affected members, in addition to the less extensive ophthalmoscopically apparent fundus findings and milder degrees of elevated rod final thresholds on dark adaptation, are more consistent with a dominantly inherited form of pigmentary dystrophy than with an autosomal recessively inherited form of dystrophy, as seen in Usher's syndrome. Moreover, if variable expressivity is presumed, dominant inheritance is further suggested by the possibility of 3 generation transmission. A marked variability in expressivity is consistent with a Mendelian dominant form of inheritance. Although speculative, in our judgment family A could be affected by 2 separate and distinctly different genetic diseases, one being an autosomal recessive form of congenital deafness and the other an autosomal dominant form of pigmentary dystrophy.

In family B, reported by the same authors, 2 of 3 heterozygotes tested were found to have elevated rod final thresholds of 1 and 2 log units. Although the technique of testing in the subjects was not cited, in most instances an elevated rod final threshold of 2 log units would be associated with a subjective complaint of nyctalopia. Neither of these two subjects, IX-1 or IX-2, complained of night blindness. Further, the absence of subjective complaints and the normal electroretinogram findings in the presence of the apparent elevation in rod final thresholds suggest that the young ages of these patients, 10 years and 7 years, may have contributed to the abnormal findings on dark adaptation, since accurate performance on dark adaptometric testing necessitates an attentive, co-operative subject.

In family C, described by De Haas and co-workers, 2 subjects, III-1 (age 71 years) and III-2 (70 years), were found to have elevated rod final thresholds of 1 and 1·5 log units, respectively. Only subject III-2 complained of nyctalopia. Subject III-1 was cited as having nuclear cataracts. Two additional family members, V-7 and V-8, showed only minimal (0·5 log units) elevation of rod final thresholds.

Since age is a factor in determining the significance of rod final thresholds, important variables such as pupillary diameter and degree of lens opacities must be considered in the interpretation of rod final threshold values. The authors did not state how these important variables were considered in their 2 heterozygous subjects who were in their eighth decade of life. Since they did not indicate either the specific manner in which thresholds were measured on the other 2 subjects with minimal degrees of elevation (for example, size of the test target, locus of the retina being tested) or their range of normal values, it was difficult to interpret the significance of a 0·5 log unit elevation.

Holland *et al.* (1972) reported gyrate-atrophy-like changes in 2 sisters (ages 80 and 75 years), one of whom was a definite heterozygote for Usher's syndrome while the other had a 50% probability of carrying the gene for this disease. Both sisters were aphakic and highly myopic. Only 1 complained of night blindness and showed an elevated rod final threshold on dark adaptation testing. The abnormal fundi and abnormal electroretinogram amplitudes noted in these 2 subjects are typical of those seen in high myopia unassociated with the autosomal recessively inherited genetic disease gyrate atrophy of the choroid and retina. The late onset (age 50) of nyctalopia in one of these 2 sisters and the absence of this symptom in the other are highly inconsistent with gyrate atrophy of the choroid and retina. The onset of nyctalopia is apparent in the majority, if not in all, gyrate atrophy cases by the second and third decade of life.

A third case cited by the same authors was that of a 16-year-old male heterozygote who was also myopic and showed a minimal (0·2 log unit) elevation of rod final threshold on dark adaptation testing. This patient showed two 1·5 disc diameter circular areas of peripheral choroidal atrophy in his right eye, which suggested to Holland and coworkers phenotypic similarities to early changes of gyrate atrophy. The patient, however, did not complain of nyctalopia. The fundus changes and minimal degree of dark adaptation elevation are consistent with the patient's 5 to 6 dioptres of myopia, and particularly in the absence of night blindness, most likely do not indicate early changes of gyrate atrophy of the choroid and retina.

Our ophthalmological findings are not consistent with those of Kloepfer *et al.* (1966), who found signs of retinitis pigmentosa and cataract in 13% of 31 known carriers of Usher's syndrome. It is noteworthy that with only a few exceptions a 'slight' hearing impairment measured audiometrically was found by these authors in known heterozygous carriers. In a previous publication Hallgren (1959) could not detect an increased prevalence of eye disease in heterozygotes. Data regarding the prevalence of hearing impairment in carriers were cited as being inconclusive.

From our study of 14 patients heterozygous for Usher's syndrome and a review of the pertinent literature we conclude that neither ophthalmoscopically apparent abnormalities nor raised dark adaptation cone or rod thresholds will be of value in identifying carriers of this disease.

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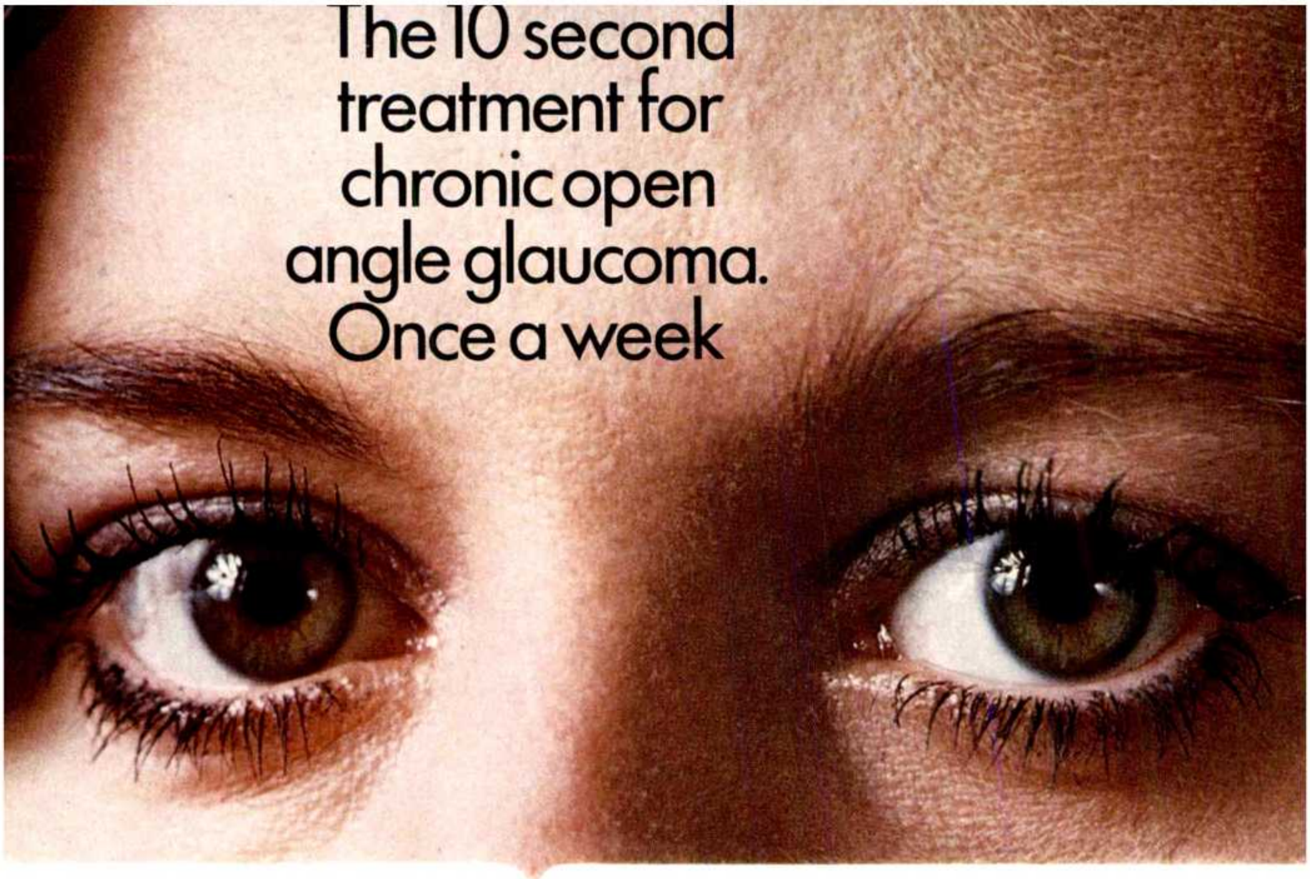
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A scanning electron microscopic examination of retinoblastoma in tissue culture

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SUMMARY Tissue cultures were established from 6 retinoblastomas and the cultured cells examined by scanning electron microscopy. Cells from cultures of normal fetal retinal and glial tissue were also examined by SEM. Though a number of different cell types were found to coexist in the retinoblastoma cultures, most had the features of cells of either glial or neuronal origin. Evidence of further differentiation of cells in each series was seen. These findings indicate that the cell of origin in retinoblastoma is a multipotential stem cell which, though neoplastic, is still capable of differentiation into both glial and neuronal series.

Retinoblastoma is a highly malignant tumour of childhood. It differs from most other human malignancies in that it is commonly transmitted as a dominant heritable trait. It is often bilateral and may be present at birth. If treated promptly it is often completely cured, and spontaneous regression may occasionally occur.

Originally retinoblastoma was thought to be a tumour of glial tissue (Virchow, 1864), but recent authors have proposed that it arises in the retinal photoreceptors (Popoff and Ellsworth, 1971; Reid *et al.*, 1974).

Reports from various cell culture studies of retinoblastoma tissue have suggested that the cells are mainly fibroepithelial with occasional cells of a more ganglion-like appearance (Huang *et al.*, 1970; Prop *et al.*, 1975). Others have reported clumps of small cells forming on a carpet of fibroepithelial cells (Reid *et al.*, 1974). These cells may then float free in the tissue culture medium in the form of small clumps. When examined by transmission electron microscopy (TEM) these small cells have an ultrastructure similar to photoreceptor cells. Popoff and Ellsworth (1971), using a double-slide technique, have shown that these small cells form Flexner-Wintersteiner rosettes and have also confirmed an ultrastructure like that of photoreceptors.

Tissue culture, with scanning electron microscopy (SEM) as an adjunct, enables a more precise classification of cell morphology. It is also hoped that in the future tissue culture sensitivities may play an important role in chemotherapeutic assessment.

In this study tissue was cultured from retinoblastoma, fetal retina, and fetal brain. We used conventional cell culture techniques and examined the cultured cells by SEM. We hoped that the greater magnification and depth of focus of SEM would show surface topography and contribute towards a clarification of the cell types seen in each culture.

Material and methods

The clinical details of 6 children with retinoblastoma from whom material for tissue culture was obtained are shown in Table 1. In each case the diagnosis was confirmed histologically. Normal fetal avascular peripheral retinal tissue was obtained from a 2-week premature infant who died 6 days after birth. Cultures from 3 specimens of normal fetal glial tissue were made in the standard way.

PRIMARY CULTURE METHODS

Fragments of retinoblastoma apparently free of necrotic areas were selected immediately after enucleation and were placed in a small volume (5 ml) of complete growth medium. The tissues were received in the laboratory within 30 minutes of removal and were handled immediately. Since retinoblastoma tissues are prone to disruption by vibration during transit to the laboratory, there was often a rich suspension of cells ready for seeding. The remaining fragments of the tumour were trans-

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Table 1 *Clinical details of 6 children with retinoblastoma from whom tissue was obtained for culture*

	Age at diagnosis	*Family history*	*Site of tumour*	*Management*	*Outcome*
Case 1	6 months	Nil	Bilateral	Left enucleation* Right irradiation	Alive and well 4½ years
Case 2	6 months	Nil	Unilateral Optic nerve infiltration	Right enucleation*	Alive and well 3½ years
Case 3	16 days	Mother and sibling	Bilateral	Right enucleation* Left irradiation	Alive and well 16 months
Case 4	4 months	Nil	Unilateral	Left enucleation*	Alive and well 15 months
Case 5	2½ years	Nil	Bilateral	Left enucleation* Right irradiation	Alive and well 4 years
Case 6	17 months	Nil	Unilateral Optic nerve infiltration	Left enucleation*	Alive and well 6 years

*Tumour tissue cultured.

ferred to a small plastic Petri dish and carefully hand-cut with a scalpel using a rocker action to give fragments of 0·5 mm cross-section with clean-cut surfaces. These were placed on the floors of plastic Petri dishes (Falcon 50 mm) or plastic culture flasks (Falcon 25 cm^2).

The fragments were well separated from each other and covered with small volumes of 0·2 to 0·4 ml of growth medium. After 60 to 90 minutes many fragments had adhered, and the vessel could then be filled carefully with medium to a depth of 1 mm without dislodging the adherent fragments. The cultures were incubated at 36°C in an atmosphere of humidified 5% CO_2. The original Petri dish in which the dissection was made was also given growth medium, as many tissue fragments were firmly anchored to furrows cut in the plastic during dissection.

The small fragments, and many of the single cells, attached and proliferated to form islets of outgrowth of cells of various shapes. Moreover, many of the dispersed cells failed to adhere, but some of these appeared viable even 7 to 10 days later. It was confirmed that these were viable by their ability to exclude trypan blue. And so, at the time of routine medium changing of the attached cell cultures, cells in the supernatant medium were recovered by centrifugation; they were then reseeded with fresh medium to new vessels and maintained as 'hover' cultures in much the same manner as lymphoblastoid cells established from human blood.

For some studies primary cultures were planted on 22×22 mm glass coverslips held in sectored Petri dishes (Falcon X-plates) and cultured as described for the main cultures above.

SECONDARY CULTURE METHODS

Individual culture dishes gave from a single tumour varying yields of islets of epithelioid and fibroblastoid cells. Each also contained many smaller cells, not attached to the floor of the dish, and these were more numerous in the cultures established from suspension of cells shaken free in transit.

The latter, unattached cells were subpassaged simply by light centrifugation of the spent medium and resuspended in fresh medium in a volume sufficient to make either 1 or 2 new cultures. At later passage of these 'hover' cultures it was apparent that increasing numbers of dead cells were appearing. These were separated from the viable cells by passage through a Ficoll-Isopaque density cushion of specific gravity 1·070 g/ml. This procedure is based on that used for the separation of human erythrocytes and neutrophils from lymphocytes (Boyum, 1968), and relies on the fact that dead tumour cells become more dense than the viable cells and sediment through the density interface.

Subpassage of attached cells required the use of a mixture of trypsin (1/5000) and versene (1/4000) in phosphate buffered saline by standard methods. Some flasks of primary cultures contained predominantly cells of 1 type, and, if so, efforts were made to develop sublines of epithelial or fibroblastoid types. In each case, and in cultures of mixed cellularity, the released cells were resuspended in fresh growth medium at an appropriate cell density and cultured in several types of containers as noted above. Occasionally attempts were made to harvest islets of cells of uniform morphology so that they were free of other cells from the culture dish. This involved occluding the colony with a sterile stainless steel cylinder stuck to the floor of the dish with silicone grease, and releasing the cells with 0·1 ml volume of trypsin solution.

GROWTH MEDIUM

Although retinoblastoma cultures have been grown in media such as Eagle's MEM and BME with 10% fetal calf serum (FCS), we have preferred to use medium 1640 with 20% FCS, as this is in constant use in our laboratory for other studies. Better pH control was obtained by adding hepes buffer to 20 mM with the bicarbonate concentration held at 0·1%.

LIGHT MICROSCOPY

Cultures in plastic Petri dishes or plastic bottles were examined daily on an inverted microscope in bright field or in phase contrast (Leitz Diavert). Selected islets of cells of various types could be easily relocated on successive days and rephotographed at the lower power magnifications to show the changing appearance of the cell colonies.

For higher power phase contrast examination at the end of the culture coverslip cultures in open Petri dishes were examined either in situ with a water immersion ×50 objective, or were inverted over a well slide and examined by standard phase contrast microscopy, before or after fixation with 2% glutaraldehyde in 0·1 M cacodylate pH 7·4 buffer. For staining by either haematoxylin-eosin or Giemsa coverslip cultures were preferred, but occasionally these were not available. The cultures of normal retina and fetal glial tissue were performed in a similar fashion.

SCANNING ELECTRON MICROSCOPY

Glass coverslip or plastic surface islets of cells, fixed in glutaraldehyde as above, were postfixed in 1% osmium tetroxide in phosphate buffer and dehydrated through ascending grades of ethanol, ending with 3 changes in absolute ethanol. They were processed according to the camphene technique of Watters and Buck (1971), which avoids tissue shrinkage by bypassing the air-liquid interphase. The coverslips were glued to the specimen stubs; a layer of gold approximately 20 nm thick was evaporated on to the surface, and the specimens were examined in a Cambridge Stereoscan Mark II at an accelerating voltage of 20 kV.

Results

Areas of interest from the tissue cultures were marked so that the same cells could be identified and examined by SEM. A wider range of cell types in retinoblastoma was revealed by SEM than is usually appreciated by light microscopy.

The distribution of cell types in each case of retinoblastoma, and in other tissue cultures examined, is shown in Table 2.

The cells were classified into the following types.

Table 2 *Distribution of cell types found by SEM of tissue culture of retinoblastoma, normal retina, and fetal brain*

	Retinoblastoma							*Fetal brain*		
Cell type	*Case number*						*Normal retina*	*Case number*		
	1	*2*	*3*	*4*	*5*	*6*		*1*	*2*	*3*
1	x	x	x	x	x	x	x	x	x	x
(a)		x					x			
(b)					x		x			
2	x		x			x	x			
3	x	x	x	x	x	x	x	x	x	x
4	x	x	x				x			
5			x				x			
6					x		x			
7		x								
8	x	x	x							
9							x			

Type 1. Fibroepithelial cells were the predominant cell type in each culture of retinoblastoma. Their size ranged from 20×120 to 120×200 μm, and the shape varied from round to spindle (Figs. 1a, 1b). Occasionally these cells had a stellate outline. The nucleus was round or elongated, and had 1 to 4 prominent nucleoli. Frequently the cytoplasm showed many intracellular fibrils, sometimes in parallel bundles and occasionally associated with what we considered to be junctional complexes. In some instances these fibrils seemed to pass extracellularly to join other cells. Occasionally, the fibrils were much longer and overlaid intermediate cells to reach a more distant cell. These cells were found in isolation in small, tightly-bound groups, in a loosely packed monolayer, or as a tightly packed irregular duolayer.

In one retinoblastoma culture (no. 2), and in the normal fetal retina, cells which were otherwise indistinguishable from those described, were seen with a single thick process of 5×150 μm, which formed an interwoven network, the processes ending on a similar cell. These cells were designated 1(a).

Cells with a markedly stellate appearance were also seen, indistinguishable from other type 1 cells, except for their stellate configuration. These were found in one case (retinoblastoma no. 6) and in normal retina, and were designated 1(b).

Type 2. A number of elongated cells were seen (Fig. 2). Their size ranged from 12×70 to 20×200 μm. These cells were much thinner than the type 1 cells. They had a tendency to form fibrils which originated at the ends of the cell and attached to

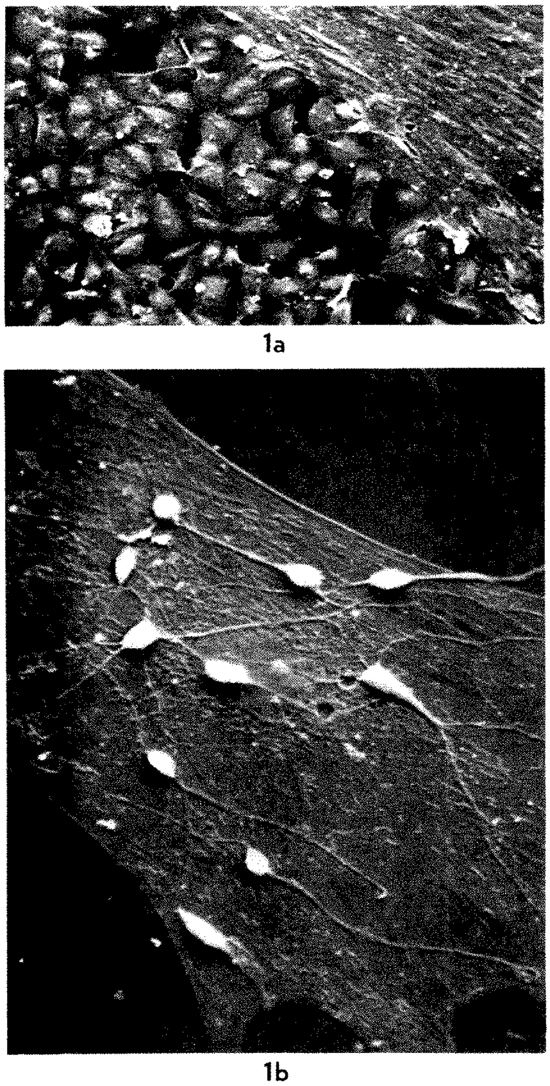


Fig. 1 *SEM photomicrograph of type 1 cells.* (a) *Cells with interweaving thick processes cluster adjacent to an area of tightly packed type 2 cells* (× *70*). (b) *An isolated type 1 cell near the edge of the culture with several type 3 cells overlying it* (× *430*)

type 1 cells. Although these cells were very similar to type 1 cells, the cell outline did not represent a continuous spectrum with type 1 cells.

Type 3. Cells in this group were characterised as having a small, oval, or rounded cell body, 5 × 15 to 15 × 25 μm in size (Figs. 3a, 3b, 3c). Sometimes they formed grape-like clusters where all the cells were without processes. Around the base of these clusters similar cells were seen, though these cells possessed a variable number of processes. These processes were 1·5 μm in thickness and up to 150 μm long. Some processes appeared to terminate on type 1 cells by means of a thickened club-shaped foot, but others seemed to blend into the cells. In every case these cells were associated with type 1 cells and almost always growing on top of these cells (Fig. 1b, 3a, 3b, 3c).

Type 4. These small rectangular cells, 10 × 30 μm in size, were characterised by numerous vesicles of various size erupting from the surface. Both thick and fine processes trailed from the poles of these cells (Fig. 4).

Type 5. These cells were long and very thin, 3 × 120 μm in size, with an elongated nucleus in the middle of the cell. One end was expanded and ended on a type 1 cell (Fig. 5).

Type 6. A number of cells were characterised by an extensive fringe of fine fibrils (Fig. 6). These flat, round cells were 50 × 100 μm in size. Their cytoplasm contained many small granules. They were always associated with type 1 cells.

Type 7. Cells of this type formed tightly packed monolayers. They were flat, 30–35 μm in diameter, roughly hexagonal in shape, and appeared to form junctional complexes with each other (Figs. 7a, 7b). They were separated into 2 subtypes: (*a*) those with obvious junctional complexes and smooth surfaces, and (*b*) those in which the cell surfaces were felt-like in appearance, and which resembled the basal surface of normal adult retinal pigment epithelium examined by SEM.

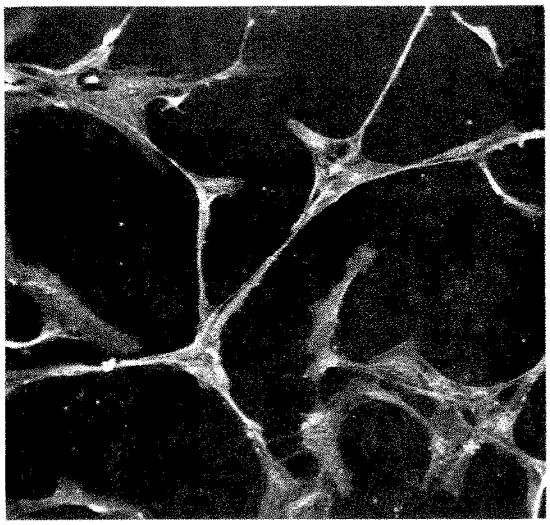
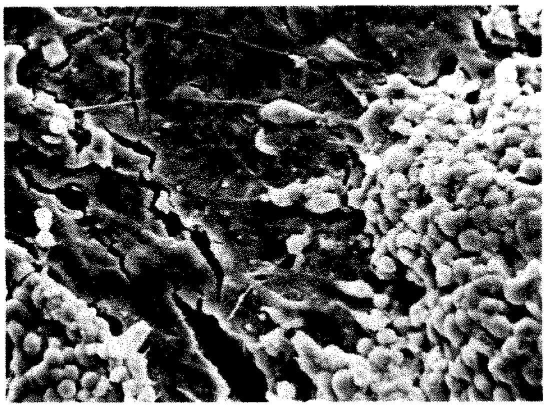
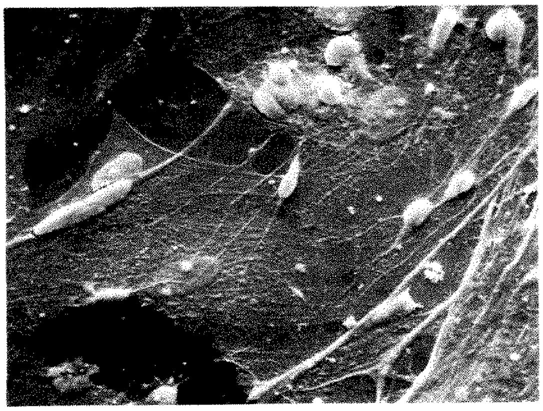


Fig. 2 *SEM photomicrograph of type 2 cells. A loose network is shown of thin, elongated cells of fibroblastic appearance* (× *125*)



3a

Fig. 3 *SEM photomicrograph of type 3 cells.*
(a) *To the right, a tightly packed group of type 3 cells cluster on top of a duolayer of type 1 cells. More elongated type 3 cells with processes can be seen near the base of the cluster* (× *260*). (b) *A spectrum of type 3 cells showing varying numbers of processes overlying type 1 cells* (× *340*). (c) *Less frequently type 3 cells with multiple processes are seen overlying type 1 cells* (× *1340*)



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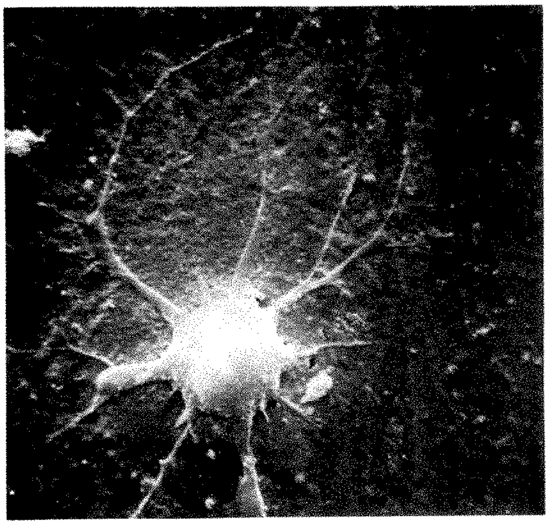

3c

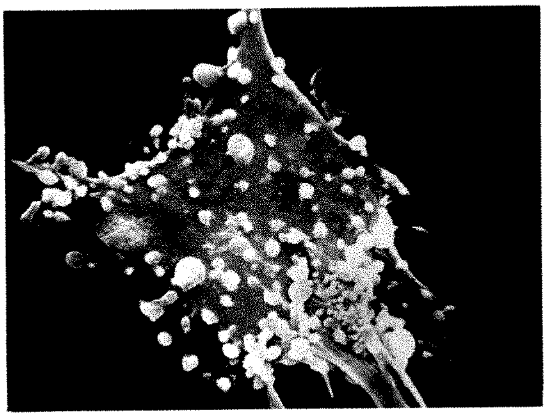

Fig. 4 *SEM photomicrograph of type 4 cells. These are small, almost rectangular cells with both fine and thick processes. The bodies of the cells had numerous vesicular-like protrusions across the membrance surface* (× *1070*)

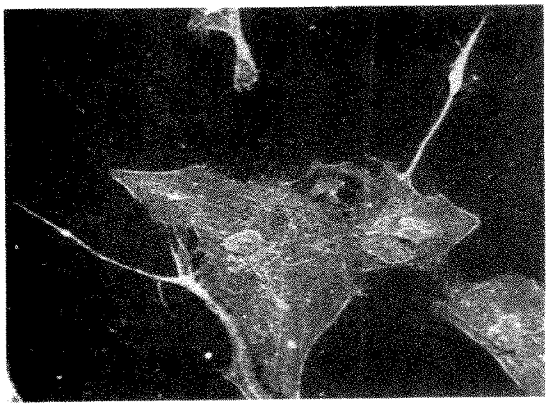

Fig. 5 *SEM photomicrograph of type 5 cells. Type 5 cells are elongated with a central nucleus. One end is conical and the other attached to a type 1 cell with an expanded foot* (× *145*)

Type 8. These small round cells, 10–20 μm diameter, with a very ruffled surface, had some longer fibrillar processes (Fig. 8). They were distinguished from type 3 cells by their irregular surface and from type 4 cells because they were rounded and raised.

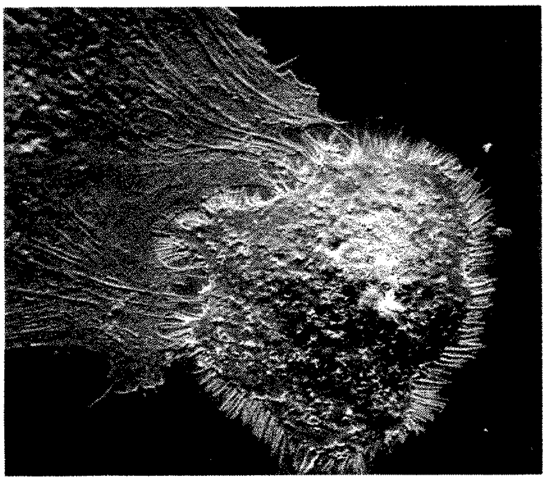
Fig. 6 *SEM photomicrograph of type 6 cells. These cells have a 'fringe' of short, fine processes and a granular cytoplasm. They are in close association with type 1 cells* (× *670*)

Type 9. Small round cells in tight clusters were seen only in normal retina (Fig. 9). These cells were 5 μm in diameter, and tended to have one short process.

Discussion

Positive identification of cells grown in tissue culture is not always easy. The external appearance of these cells may differ from normal cells because of the different pattern of growth on a flat surface, compared with the three-dimensional cell-to-cell relationship found in solid tissue. Further differences can be produced by variations in tissue culture conditions and media. In some cases identification may be aided by using special stains or specific enzyme assays. The difficulty in identifying cells is shown in the following example.

In light microscope studies of normal retina in tissue culture Liss and Wolter (1961), using human tissue, and Hansson and Sourander (1965), using rat tissue, considered a specific cell to be a ganglion cell. Hild and Callas (1967), using their experience with rat retinal cultures, reviewed the work of these authors and considered the same cell to be glial.

Huang *et al.* (1970) reported 4 cell types in tissue cultures of retinoblastoma. One cell type they called microglial, and another resembled a fibro-

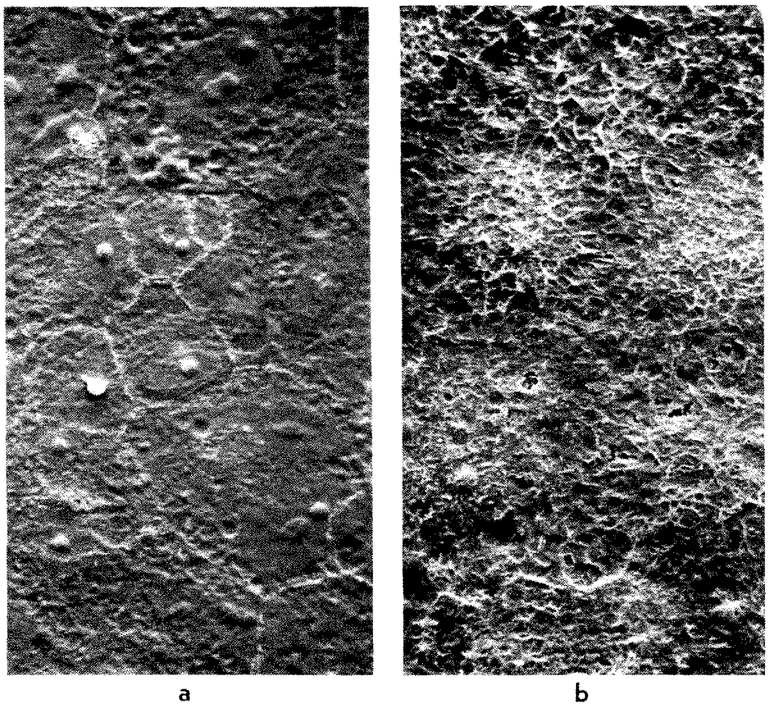

Fig. 7 *SEM photomicrograph of type 7 cells.* (a) *These cells form a close monolayer joined by obvious junctional complexes* (× *415*). (b) *While these cells form a 'carpet', their cell boundaries are not so distinct and their surface has a 'felt-like' appearance* (× *830*)

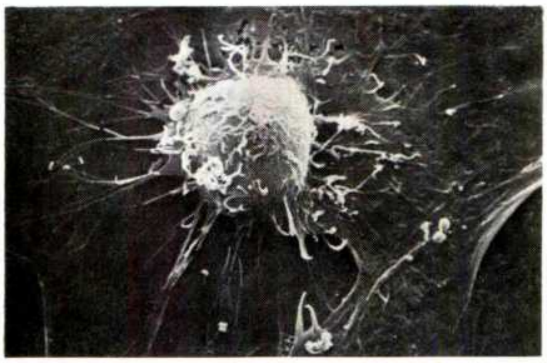

Fig. 8 *SEM photomicrograph of type 8 cells. Type 8 cells, which are rounded, with a ruffled surface and long fibrillar processes, lying over type 1 cells* (× *1195*)

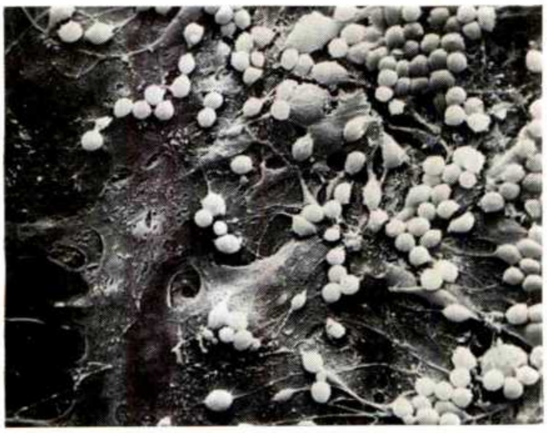

Fig. 9 *SEM photomicrograph of type 9 cells. Type 9 cells from a fetal retinal culture. These small round cells are in a cluster overlying a layer of type 1 cells. They are in close association with type 3 cells* (× *295*)

cyte. They tentatively called 2 other groups of cells ganglion cells, 1 group having long processes. On reviewing their photographs we believe the cultures to have been mainly glial, the cells called ganglion cells most probably being astroglial.

The cultures of Prop *et al.* (1975) consisted almost entirely of glial cells. They reported an interesting difference in growth pattern observed between hereditary and sporadic retinoblastoma. 'Unruhig' or unruly growth was never found in the former, while it was found in 25–50% of cultures of sporadic tumors. We did not observe this unruly growth in our cultures.

Reid *et al.* (1974) and Albert *et al.* (1974) have reported 2 distinct cell types: a large fibroblast-like or stromal cell, which forms a monolayer, and a smaller round cell, which forms clumps on the glial cells, and which may then detach to float free in the supernate. TEM of the small cells shows that they are very similar to photoreceptors.

We consider that various cell types are truly represented in our cultures, and the variations observed do not reflect the inherent changes seen within 1 cell type grown in tissue culture, particularly as distinct cell types were consistently seen occurring together in particular cultures.

Our type 1 cells are almost certainly glial. They were found in all retinoblastomas and were indistinguishable from the cells found in fetal brain cultures, which were called astroglial by Shein. (1965). They were also seen in the tissue cultures of normal retina. They resembled the ganglion cells seen by Huang *et al.* (1970) and are similar to the stromal cells of Reid *et al.* (1974).

Type 2 cells were probably also glial and were seen in retinoblastoma and fetal retinal cultures. These cells have a fibroblastic appearance and are similar to the fibroblasts of Huang *et al.* (1970). They may reflect the morphological changes reported in retinoblastoma cultures by Yoneda and Van Herick (1963) and Prop *et al.* (1975)—that is, a cyclical change from a fibroblastic to an epithelial appearance.

Type 6 cells were similar to type 1 cells in many respects, though the striking fringe set them apart. They probably represent a variant of glial cells, possibly degenerating cells. They were not seen frequently.

Type 7 cells resemble epithelial cells, possibly retinal pigment epithelium. They were agranular, but the loss of granules by retinal pigment epithelium in tissue culture has been reported by Albert *et al.* (1972). But they did not resemble the retinal pigment epithelial cells we have seen in tissue cultures of normal human retina. Alternatively, type 7 cells may be of endothelial origin. These smooth cells look similar to cultures of endothelium. If this were the case, it would be of interest, as human endothelial cells are difficult to grow without the presence of a growth factor (Gospodarowiz *et al.*, 1977). Such a growth factor may have been supplied by the tumour cells in this case. However, the exact nature of these cells is not known.

Apart from type 1 cells the cells seen most commonly were the small round cells called type 3 cells. They may represent a heterogeneous group, as they include cells without processes and those with many processes. However, a continuous spectrum of cells was seen in this group. They were also seen in fetal brain cultures and were similar to those cells labelled spongioblasts by Shein (1965). In retinoblastoma cultures they undoubtedly represent the small cells which have been shown by Reid *et al.* (1974) to have an ultrastructure closely related to photoreceptors. Similar cells have been called small ganglion cells by Hansson and Sourander (1965), bipolar cells by Pomerat and Littlejohn (1956), and neurones by Lodin *et al.* (1973). True rosette formation could be confirmed only by sectioning clumps of these cells. However, the arrangement of these clusters resembled the clumps of cells described by Ohnishi (1974), using SEM, which he demonstrated by TEM to be rosettes. Craft *et al.* (1978) have reported similar findings.

Type 5 cells had a morphological appearance similar to isolated photoreceptor cells. These cells had an elongated outline and a central nucleus. One end was conical and the other had an expanded foot, which attached to a type 1 cell.

Type 4 cells had the appearance of small neurones. Type 8 cells were similar to the cultured macrophages seen by SEM but differed from these both in the greater length and in the relative poverty of the processes. The nature of these cells is not known, but Ben-Shaul and Moscona (1975) have labelled similar cells seen in chick retinal culture as neurones.

Type 9 cells were seen in normal retina only and probably represent normal neuroblasts. They differ from type 3 cells because they are smaller, more uniform in size and shape, and have clean, well-defined surfaces.

There did not appear to be any particular cell type associated with sporadic or familial tumours, nor was there a correlation between the cell types present and bilaterality or optic nerve infiltration by the tumour.

Shein (1965) has shown that in normal fetal glial culture, small round cells, presumably spongioblasts, can differentiate into large fibroepithelioid cells, which he called astrocytes. Elul *et al.* (1975), working with neuroblastoma, noticed that small round cells differentiated into larger cells.

Our findings suggest that retinoblastoma is indeed a tumour of primitive small round stem cells which may have the capacity to differentiate into both neuroblasts and spongioblasts.

If one postulated the differentiation of the retinoblastoma cell to spongioblasts and then to glial tissue, it would explain the predominantly glial nature of so many of the tissue cultures of retinoblastoma; for, although glial cells are not prominent in retinoblastomas examined histologically, they do form a large proportion of the tissue in culture. The preponderance of glial cells is seen even in the early passages, when glial 'overgrowth' is unlikely. Why there should be this predominance of glial elements in tissue culture and not in vivo is not fully understood. It may well be that factors in the tissue culture system favour glial differentiation at the expense of neuronal differentiation. In this study every effort was made not to discard unattached cells.

Evidence of the capacity for progressive differentiation of retinoblastoma into neuronal elements is seen in sectioned tumour tissue. Rosettes composed of primitive photoreceptor cells are a relatively common finding, while the more highly differentiated photoreceptor cells forming fleurettes are less common (T'so *et al.*, 1970). Further differentiation is shown by synapse formation, though this is rarely seen (Dickson *et al.*, 1976).

Thus there is both in-vitro and in-vivo evidence of progressive differentiation of retinoblastoma cells into cells of both the glial and neuronal series, and therefore it is reasonable to postulate that the retinoblastoma cell is in fact a stem cell which can give rise to cells of both these series. That retinoblastoma may be derived by a multipotential stem cell is not new. It was first suggested by Ginsberg in 1899 as quoted by Duke-Elder (1967). However, many of the recent studies of retinoblastoma have been directed towards confirming the photoreceptor-like nature of some cells in the tumour and therefore its neuronal origin (Popoff and Ellsworth, 1971; Reid *et al.*, 1974). This has resulted in less attention being paid to the glial elements present in this tumour.

Although an examination of tissue culture cell surfaces, even at the great magnification attainable by SEM, cannot always elucidate the true origin of cells, the morphology of the cells indicates that retinoblastoma is truly a tumour of primitive cells, which have the potential to differentiate into spongioblasts and other glial cells as well as neuroblasts and other neuronal cells, including photoreceptors.

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Retinoblastoma: correlation of invasion of the optic nerve and choroid with prognosis and metastases

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SUMMARY The histological sections of 74 retinoblastoma patients were reviewed. The extent of optic nerve invasion was correlated with choroidal/scleral extension. Choroidal invasion carries 100% survival provided that the sclera, iris, and whole optic nerve are not also involved. Invasion of the optic nerve beyond the lamina cribrosa also carries 100% survival provided that the resection line is free and that invasion does not involve the sclera or iris. Plentiful rosettes were usually found in those tumours that had not extended beyond the choroid or as far as the resection line of the optic nerve and were therefore associated with a good prognosis. The absence of rosettes did not necessarily indicate a poor prognosis. The site of metastases was related to optic nerve and scleral/extrascleral extension. The various systems of staging retinoblastoma are compared, and a new system is proposed to cover the whole spectrum of the disease and to offer a reliable guide to prognosis and treatment.

Retinoblastoma is generally accepted as having an increasing mortality which correlates with the extent of invasion of the optic nerve, as judged by histological examination of the nerve after enucleation (Brown, 1966). It has been shown that the prognosis becomes significantly worse once the tumour has extended past the lamina cribrosa (Carbajal, 1958; McKenzie in Zimmerman, 1961; Brown, 1966). Invasion of the choroid by retinoblastoma is also considered to be a poor prognostic sign (Carbajal, 1958; McKenzie in Zimmerman, 1961; Brown, 1966; Herm and Heath, 1956; Miron *et al.*, 1966; Taktikos, 1966; Duke-Elder, 1967; Sevel *et al.*, 1974).

The first 3 of these authors showed that the mortality rate increased with increasing involvement of the choroid. Redler and Ellsworth (1973), however, found by examining serial sections of the eyes that choroidal invasion was both more common and less dangerous than previously believed.

The purpose of this study was to see whether our findings conformed with those of other authors with regard to optic nerve and choroidal extension and, if so, to see if a more accurate prognosis could be obtained by the correlation of one with the other. The findings in this direction have led us to formulate a new clinicopathological staging system which we consider to be a useful guide to prognosis and treatment.

Clinical data

Between 1952 and 1975, 95 patients with retinoblastoma were referred to the Ocular Tumour Clinic at Groote Schuur Hospital, Cape Town; 26 (27%) of these patients had bilateral disease. Two patients who presented with advanced unilateral disease subsequently developed tumour in the opposite eye as a result of direct spread from one optic nerve to the other via the optic chiasma. They have been included in the unilateral group. None of the patients gave a family history of retinoblastoma, although 2 patients each had 1 parent with a healed unilateral retinal scar, and 1 patient with unilateral retinoblastoma has since had a child who developed retinoblastoma.

The histological sections of 74 patients were reviewed; 17 of these had bilateral disease, and in 11 cases both eyes were available for histological examination. These patients have all been followed up for a minimum of 3 years or until death. Twenty-one (22%) were excluded from the survey because there was insufficient histological material or inadequate follow-up. The slides were 5 μm thick and stained with haematoxylin and eosin. Further

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sections were required for the evaluation of 15 eyes. Serial sections were not done.

Three of the 57 unilateral cases received no further treatment. Seven patients received deep *x*-ray therapy to the orbital contents and apex of the orbit, and 41 patients were treated with prophylactic cytotoxic drugs in addition to orbital irradiation (Sealy, 1977). Five patients were treated with chemotherapy and orbital and craniospinal irradiation because they were found to have a positive brain scan and/or malignant cells in the cerebrospinal fluid (CSF). One patient had an exenteration and chemotherapy for advanced local disease.

Four of the 17 bilateral cases had bilateral enucleations followed by orbital irradiation; 3 of these also received prophylactic chemotherapy. One patient had bilateral enucleations followed by orbitocranial irradiation and chemotherapy because of a positive brain scan and CSF cytology. After enucleation of the more severely affected eye in the remaining 12 patients the second eye was treated with external irradiation and chemotherapy. In addition a radioactive tantalum plaque was used in 5 patients. Four of these 12 patients subsequently experienced local treatment failure, requiring enucleation, and 2 further patients were similarly treated for vitreous haemorrhage and secondary glaucoma.

Staging

Because of the advanced stage of the tumour in the eyes of many of our patients we have not been able to use the scheme proposed by Reese and Ellsworth (1963) and therefore use the following system:

Stage I. Lesions amenable to local therapy.

Stage II. Lesions unsuitable for conservative local therapy but still ostensibly confined to the eye and orbit.

Stage III. Lesions which have spread beyond the orbit, that is, to local lymph nodes, adjacent bones, or to the central nervous system, but have not yet undergone blood-borne metastases.

Stage IV. Lesions which have undergone haematogenous metastases.

Stage I is a clinical staging and treatment is aimed at preserving vision. Enucleation is indicated in stage II, and its substages are based on the histological examination of the enucleated eye. For the purposes of this analysis, the following dual substage system has been adopted. Stage II: substages N0, N1, N2, N3; substages C0, C1, C2, C3*a* and *b*, C4*a*, *b*, and *c*. The first substage is based on nerve involvement and was the system used by McKenzie in Zimmerman (1961) (0, I, II, III). The second substage is based on involvement of the rest of the eye. The choroidal involvement is based on McKenzie in Zimmerman's (1961) classification, but it is extended to include involvement of the anterior uvea and sclera.

STAGE II

N0: *Nerve negative*—no tumour in the optic nerve.

N1: *Anterior lamina cribrosa*—tumour invasion of the optic nerve head up to or in the lamina cribrosa but not extending beyond it.

N2: *Posterior lamina cribrosa*—tumour invasion beyond the lamina cribrosa but not as far as the resection line.

N3: *Whole nerve*—tumour involvement of the nerve right up to the resection line, or when the optic nerve was not visualised but convincing radiological evidence of optic foramen erosion was present.

N?: Stage of nerve unknown. No nerve present in multiple sections examined.

C0: *Choroid negative*—no tumour involvement of the choroid.

C1: *Superficial choroid*—tumour involvement of the superficial layers of the choroid up to half its thickness.

C2: *Deep choroid*—tumour involvement of the whole thickness of the choroid without penetration of the sclera, ciliary body, or iris.

C3*a*: *Into sclera ± ciliary body*—tumour involvement of the full thickness of the choroid with penetration of the sclera. The ciliary body may or may not be involved, but the iris and anterior chamber are free of tumour.

C3*b*: *Into sclera, ciliary body, iris, and anterior chamber*—tumour involvement of the full thickness of the choroid with penetration of the sclera and tumour either in or replacing the ciliary body, iris, and anterior chamber.

C4*a*: *Through sclera ± ciliary body*—tumour extension right through the sclera. The ciliary body may or may not be involved but the iris and anterior chamber are free of tumour.

C4*b*: *Through sclera, ciliary body, iris, and anterior chamber*—tumour extension right through the sclera and tumour either in or replacing the ciliary body, iris, and anterior chamber.

C4*c*: *Eye disorganised*—total destruction by tumour. The nerve was recognisable in 5 out of 9 cases.

Results

Table 1 correlates survival with the extent of tumour spread down the nerve and with extension into the choroid, sclera, and anterior uveal tract. In bilateral cases, in which both eyes were available

Table 1 *Retinoblastoma—3 year survival correlated with tumour extension in 74 patients*

Alive / Dead	N 0		N1		N2		N3		N?	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
C0	5		10		3					
C1	2		5		1		2			1
C2	1		4		2		2	2	2	
C3a					1		1	3		
C3b							1	3		
C4a					1			2	2	1
C4b				1		1		6		
C4c	1							4	2	2

for histological examination, for the purposes of correlating the stage of the disease with survival each substage was based on the greater degree of tumour involvement of the 2 eyes considered together. The results show that the 3-year survival is 100% for all cases up to stage N2, C2 (33 patients), i.e., provided the resection line of the nerve is free of tumour and provided also that tumour involvement of the choroid does not extend into the sclera, ciliary body or iris.

Beyond stage N2, C2 the overall survival is 34% (38 patients, N2, C1, and C2 patients excluded). Survival in stage N3 alone is 23% (26 patients), and in stages C3 and 4 alone it is 28% (32 patients).

Four patients had C4*a* lesions with ciliary body involvement. Three of them have survived for 4, 6, and 13 years respectively. Tumour involvement of the ciliary body and iris was seen in 13 patients and was always accompanied by extension into the anterior chamber. It was also accompanied by choroidal and scleral extension, except in 1 case where there was only superficial choroidal involvement. This patient has survived 23 years, but there are only 2 survivors among the other 12 patients.

Three out of 9 patients in whom the eye was totally destroyed have survived 4, 12, and 16 years respectively.

Histological evaluation included recording the presence or absence of true Flexner-Wintersteiner rosettes in the tumour (Table 2). Among the bilateral cases, where both eyes were available for examination, 5 patients were excluded because there was a difference in rosette status between the 2 eyes and they therefore could not be evaluated in terms of survival. The other 6 bilateral cases were included because both eyes showed the same features, that is, bilateral presence or absence of rosettes.

Plentiful rosettes were seen in the eyes of 12 patients, occasional rosettes in the eyes of 6 patients, and no rosettes in the eyes of the remaining 51 patients. One of the 12 patients in whom plentiful rosettes were seen died. This patient had an N2, C4*b* tumour. The remaining 11 patients, with tumours ranging from N0, C0 to N2, C2, all survived 3 years or more. Among those patients in whom no rosettes were present all those with tumours up to N2, C2 survived and 9 (29%) of those with tumours beyond N2, C2 also survived. The difference in survival between those with and those without rosettes is statistically significant at the 5% level.

METASTASES

The cause of death was unknown in 6 of the 26 patients who died, and no metastases were recorded. Of the remaining 20 patients necropsies were performed on 13, and in 7 patients who did not have a necropsy there was clinical, histological, radiological, or cytological evidence of tumour spread.

Metastases have also been seen in 5 patients who are alive, their disease being controlled by irradiation and long-term chemotherapy. Metastases in these 25 patients (20 dead, 5 living) have been divided into the following groups: (1) Metastases of the central nervous system (CNS). Intracranial metastases, tumour involvement of the spinal cord or meninges. (2) Distant metastases—blood-borne metastases in the bones or viscera, tumour in the distal lymph nodes. (3) Local disease—recurrent disease in the orbit or adjacent bones, local lymph node involvement (preauricular, cervical, or submandibular).

There is some dispute whether skull lesions are the result of lymphatic spread (Meighan and Michaelson, 1938; Duke-Elder, 1967), direct dissemination (Merriam, 1950; Knapp in Merriam, 1950; Carbajal, 1959), or haematogenous spread (Merriam, 1950; Carbajal, 1959). In this series there

Table 2 *Relationship of rosettes to survival in 69 retinoblastoma patients*

	Number of patients			
	Total	*Survived 3 years*		*Dead*
	69	*Up to N2, C2*	*Beyond N2, C2*	*All beyond C2, N2*
Plentiful rosettes	12	11	—	1
Occasional rosettes	6	2	2	2
No rosettes	51	20	9	22

Table 3 *Relationship of metastases to whole nerve and scleral/extrascleral involvement*

		Metastases						
Stage	*Total number of patients*	*CNS only*	*CNS plus local*	*CNS plus distant*	*CNS plus distant plus local*	*Distant only*	*Distant plus local*	*Local only*
N3	16	4	4	1	5	1	1	—
C3 C4	21	3	4	1	7	—	3	3

was 1 case with local disease and a skull lesion but no other evidence of distant disease; it has been included in the local disease group. In another case there was involvement of the frontal and parietal bones, alveolus, and left tibia, but no evidence of local orbital recurrence or lymph glands; this has been placed in the distal group. Two other cases had involvement of the alveolus and masseter respectively, again without evidence of local orbital recurrence or lymph glands. They have also been placed in the distant or haematogenous group. The remaining 5 cases with skull metastases had evidence of both local and distant disease and have therefore been included in both groups.

Metastases were seen as follows: CNS only, 5; CNS and local, 4; CNS and distant, 1; CNS, distant and local, 7; distant only, 2; distant and local, 3; local only, 3; total, 25. Table 3 summarises the site of metastases in relation to whole nerve and scleral/extrascleral involvement.

The whole nerve was involved in 16 of these 25 patients. CNS metastases were found in 14 patients (87·5%), distant metastases in 8 (50%), and local disease in 10 patients (62·5%). Two patients who had CNS metastases and are alive have now survived 5½ years (previously reported by Stannard *et al.*, 1975) and 2 years respectively, having been treated by irradiation and long-term chemotherapy.

The sclera and extraocular tissues were involved in 21 of the 25 patients. CNS metastases were found in 15 (71%), distant metastases in 11 (52%), and local disease in 17 patients (81%). Two C2 patients developed metastases. One of these (C2, N3) died of distant metastases, and the second (C2, N1) developed a metastasis in the masseter muscle 5 years after initial therapy. This has been controlled for 11 months with local deep *x*-ray therapy and chemotherapy. Yet another patient (N2, C4*a*) developed a mass in the ipsilateral temporal fossa and cervical gland—both proved histologically to be recurrent retinoblastoma—4 years after initial treatment. He has survived for 2 years after irradiation and prolonged chemotherapy. The latter 2 cases emphasise the importance of continued observation of these patients.

Twelve of the 13 patients with distant metastases died. The iris was involved or replaced in 8 of them (62%). In the remaining 12 patients who did not have distant metastases the iris was involved or replaced in 7 patients (58%).

Discussion

The frequency of bilateral disease was similar to that encountered by other authors, but the overall mortality of 39% was higher than that encountered by recent authors (Table 4). This could be attributable to the delay in presentation (Herm and Heath, 1956; Carbajal, 1958; Taktikos, 1966) (Table 5) and the late stage of presentation among our patients, many of whom are less sophisticated than those in other centres.

Table 4 *Incidence of bilateral disease and mortality of all retinoblastoma patients: review of literature*

	Total number of patients	*Bilateral disease (%)*	*Mortality of total number of patients (%)*
Callender in Zimmerman (1961)	45	25	
Duke-Elder (1940) reviewing other authors		20 to 30	
Adam			43
Leber			43
Merriam (1950)	759	27·6	
Herm and Heath (1956)	79	25	23·7
Carbajal (1958)	72	30·5	30
Reese (1963)		80	15 to 20
Howard and Ellsworth (1965)	235	59	
Jensen (1965)	69	30	23
Brown (1966)	462	57·6	31·4
Taktikos (1966)	287	39	16·7
Stafford *et al.* (1969)	618		29·9
Cassady *et al.* (1969)	230	35	20·9
Bedford *et al.* (1971)	139	80	8·3
Höpping *et al.* (1975)	228	75	6·1
Aherne and Roberts (1975)	50	46	16
Devesa (1975)	61	18	10
Present series	95	27	39

The overall average age at enucleation was 35·9 months (95 patients). The oldest patient in the series was 16 years. The average age among 3-year survivors was 31·6 months, and those who died presented at an average age of 43·7 months (Table 6). Leelawongs and Regan (1968) noted a similar difference of 24 and 32 months respectively.

Among patients with bilateral disease the average age was 17·3 months, whereas patients with unilateral disease presented at an average age of 42·8 months (Table 6). This supports the findings of a previous survey (Sevel *et al.*, 1973) and has been noted by several authors, including Dollfus and Auvert in Stallard (1955)—22 and 40 months, Mork (1961)—10 and 24 months, Jensen (1965)—15 and 29 months, Leelawongs and Regan (1968)—15 and 24 months, Knudson (1971)—15 and 32 months, Aherne and Roberts (1975)—8½ and 31 months, Lennox *et al.* (1975)—8 and 24 months, Matsunaga (1976), and Bonaiti-Pellie *et al.* (1976). The latter 2 authors also found that familial cases, whether bilateral or unilateral, presented at an earlier age than sporadic cases.

The mortality for unilateral cases was higher than for those with bilateral disease (but only at the 10% level of significance).

	Number of patients		
	Survived 3 years +	*Dead*	*Mortality*
Unilateral	38	30	44%
Bilateral	18	6	25%
Total	56	36	39%

One patient with unilateral disease and 2 patients with bilateral disease were lost to follow-up between 1 and 6 months after treatment.

The series of the Armed Forces Institute of Pathology (Reese, 1963) and Herm and Heath (1956) both found no difference in survival statistics between unilateral and bilateral cases, while Carbajal (1958) and Jensen (1965) found a higher mortality among those with bilateral disease. It should be noted from Table 4 that in some series (Bedford *et al.*, 1971; Höpping *et al.*, 1975; and Aherne and Roberts, 1975) a high percentage of bilateral cases was associated with a low mortality.

Table 5 *Review of age at enucleation and duration of symptoms in retinoblastoma*

	Average age at enucleation, in months	*Average age when symptoms appeared, in months*	*Average length of symptoms in months*
Duke-Elder (1940) reviewing other authors	24		
Falls and Neal (1951)	25·4	19·9	5·5
Herm and Heath (1956) excluding 6 year+	26·6	21·7	4·9
Carbajal (1958)	23·2	17·1	6·1
Reese (1963)	13	10	3
Howard and Ellsworth (1965)	20	16	4
Taktikos (1966)	25		
Bedford *et al.* (1971)		12	
Present series	35·9	29	6·9

The average length of symptoms (6·9 months) is higher than that found by other authors (Table 5), and this figure should probably be higher still, as the duration of symptoms was unrecorded in 18 (19%) patients. The average duration of symptoms among 3-year survivors was 5·4 months, and among those who died it was 7·9 months. The duration of symptoms among those with bilateral disease was 6 months, and among those with unilateral disease it was 7·2 months (Table 6). In 4 patients with bilateral disease tumour was seen in the second eye at an average of 10·7 months (range 3 to 18 months) after enucleation of the first eye. This delay in appearance of the tumour in the second eye has already been noted by Reese (1963), Jensen (1965), and Aherne and Roberts (1975) and indicates the importance of regular observation of the second eye.

As stated previously, it is generally accepted that the mortality for retinoblastoma increases with increasing invasion of the optic nerve (Brown, 1966) and that the prognosis becomes significantly worse once the tumour has extended beyond the lamina cribrosa (Carbajal, 1958; McKenzie in Zimmerman, 1961; Brown, 1966) (Table 7). The present series shows that, provided the resection line of the nerve is free, invasion of the optic nerve carries 100% survival for 25 patients, 6 of whom had invasion beyond the lamina cribrosa, allowing for the treatment technique utilised and provided also that tumour invasion does not go beyond the choroid.

It is also generally accepted that choroidal

Table 6 *Average age at enucleation and duration of symptoms in 95 retinoblastoma patients*

	3 years+ survivors	*Dead*	*Bilateral*	*Unilateral*
Average age at enucleation, in months	31·6	43·7	17·3	42·8
Average duration of symptoms, in months	5·4	7·9	6	7·2

Table 7 *Review of survival related to progressive invasion of the optic nerve in retinoblastoma*

Involvement of nerve	*Percentage survival*			
	Carbajal (1958), 72 patients	*McKenzie in Zimmerman (1961), 300 patients*	*Brown (1966), 204 patients*	*Present series, 64 patients*
No involvement		91·6	72·4	100
Invasion anterior to or in lamina cribrosa	83	85·2	84	100
Invasion posterior to lamina cribrosa—resection line free	33	55·6	37	100
Invasion as far as resection line		36	19	23

Table 8 *Review of survival related to choroidal involvement in retinoblastoma*

	Carbajal (1958), 72 patients	*McKenzie in Zimmerman (1961), 236 patients*	*Brown (1966), 204 patients*	*Redler and Ellsworth (1973), 42 patients*	*Present series, 74 patients*
Number of patients with choroidal involvement	26	128	85	26	15 (N3, N?, C3, C4 patients excluded)
	Percentage survival				
Superficial choroidal involvement	57	78	87·5	81	100
Full thickness choroidal involvement	0	36	40		100

invasion carries a bad prognosis (Herm and Heath, 1956; Carbajal, 1958; McKenzie in Zimmerman, 1961; Brown, 1966; Miron *et al.*, 1966; Taktikos, 1966; Duke-Elder, 1967; Sevel *et al.*, 1974), although Redler and Ellsworth (1973) found that choroidal invasion was both more common and less dangerous than previously believed (Table 8). The present series shows that whether tumour invasion of the choroid is superficial or full thickness, provided it does not penetrate the sclera, ciliary body, or iris, and provided the resection line of the nerve is free, the survival is 100% for 15 patients. The prognosis becomes considerably worse once the sclera or anterior uvea is involved in addition to the choroid.

The poor prognosis associated with involvement of the iris has previously been noted by Sevel *et al.* (1974), but it would seem that iris involvement reflects advanced disease, and it is the latter factor that is associated with haematogenous dissemination.

The incidence of choroidal invasion varies with different authors—Jensen (1965) 17%, Taktikos (1966) 20%, Reese (1963) 25%, Walton and Grant (1968) 28%, Herm and Heath (1956) 34·5%, Carbajal (1958) 36%, Brown (1966) 41·6%, McKenzie in Zimmerman (1961) 54%, Redler and Ellsworth's (1973) serial sections 62%, Miron *et al.* (1966) 83%. The incidence here of invasion of the choroid without extension into the sclera is 32·4%. Invasion of the choroid together with extension into or through the sclera occurred in a further 43·2% of patients. It is not entirely clear whether the other authors' figures for choroidal invasion included those in whom the sclera was involved in addition to the choroid (with the exception of Miron *et al.*, 1966, see below).

If they did, then it could account for the higher survival of those with choroidal invasion alone in our series. In Miron *et al.*'s (1966) series 8 of the 9 patients with choroidal invasion who died also had invasion of the emissary vessels of the sclera.

The mortality from scleral involvement (67%) is well documented by other authors—Carbajal (1958) 57%, Brown (1966) 75%; and likewise from extrascleral involvement (74%), Herm and Heath (1956) 100%, Taktikos (1966) 77%, and Brown (1966) 70%). Of the patients in this series with scleral or extrascleral involvement who died 78% (18/23) also had invasion of the optic nerve up to the resection line. In the remaining 5 patients the optic nerve was not present on the slide in 3 and the invasion did not reach the resection line in 2.

The observation that plentiful rosettes were found in the eyes of patients with an early stage of the disease and therefore indicate a good prognosis corresponds to the findings of other authors (Parkhill and Benedict, 1941; Herm and Heath, 1956; Carbajal, 1958; Brown, 1966).

The average age at enucleation among patients with many rosettes was 15 months and the average length of symptoms 4 months (Table 9). Among

Table 9 *Relationship of rosettes to age at enucleation and duration of symptoms in 69 retinoblastoma patients*

	Number of patients	*Average age at enucleation, in months*	*Average length of symptoms, in months*
Plentiful rosettes	12	15	4
Occasional rosettes	6	63·4	8·2
No rosettes	51	41·4	7·7

patients in whom no rosettes were found the average age was 41·4 months and the average length of symptoms 7·7 months. The figures in the group where occasional rosettes were seen are probably not reliable, as this was a small number of patients and included 1 child of 9 years and another of 14 years. Therefore symptoms were first noticed in patients with many rosettes at the age of 11 months and in patients with no rosettes at the age of 33·7 months.

It has been suggested that the longer the tumours are present the more undifferentiated they become, so that mortality is related to the prolonged presence of the tumour and its extension rather than the degree of differentiation (Herm and Heath, 1956; Brown, 1966). The question arises as to whether the children with undifferentiated tumours harboured their tumours for 22 months, or whether a more differentiated tumour is likely to appear in the first year or two of life.

Parkhill and Benedict (1941) distinguished two different forms of the disease—the slower-growing neuroepithelial type with rosettes, which was not usually associated with invasion beyond the nerve or orbit, and the highly undifferentiated retinoblastoma, which was associated with optic nerve and extraocular extension. Herm and Heath (1956), as mentioned above, found that the longer a tumour was present the more undifferentiated it became. Taktikos (1966) found that the degree of differentiation was unrelated to the size and therefore the age of the tumours, and suggested that well differentiated as well as less differentiated tumours seem to arise as such. Jensen (1965) noted that rosettes were found more frequently in small tumours (less than half the eyeball) than in large tumours (more than half the eyeball), although the length of history was the same for both. He suggested that the more anaplastic tumours grew at a faster rate and therefore reached a larger size before enucleation was performed. Unfortunately he does not relate the size or the degree of differentiation to the age of the patient.

Age is considered to be one of the most crucial prognostic factors in the two most common non-cerebral malignant solid tumours—Wilms's tumour and neuroblastoma (Sutow *et al.*, 1970).

The prognosis for Wilms's tumour (excluding congenital mesoblastic nephroma) is better for children under 2 years old (D'Angio *et al.*, 1976). These children are less likely to develop metastases (Sutow *et al.*, 1970), and according to Bolande (1971) metastases below the age of 1 year are rare. The degree of differentiation of the tumours is also an important factor. Anaplastic tumours are almost always found in patients over 2 years old and associated with a poor outcome (Beckwith and Palmer, 1978), whereas sarcomatous lesions are found both in the under- and over-2-year-old groups. They tend to metastasise, have a poor prognosis, and account for most of the deaths in the under 2-year-olds (Johnson *et al.*, 1967; Beckwith and Palmer, 1978).

The prognosis for neuroblastoma is also better below the age of 2 years. Metastases are less common in this age group, and although the degree of differentiation is unrelated to age those with differentiated tumours below the age of 2 years did significantly better than those with undifferentiated tumours in this age group (Sutow, 1958). After the age of 2 years the prognosis was poor for both differentiated and undifferentiated tumours.

A similar situation appears to apply to retinoblastoma, those under the age of 1 or 2 years having a better prognosis than those appearing in subsequent years. If this is so, it could account for the low mortality in a series with a younger age group, such as that of Bedford *et al.* (1971) and the higher mortality in our series, where a large proportion of tumours were in older children.

The presence of rosettes may be associated with a better prognosis *per se* or it may be merely an incidental finding in the disease in younger children who have a better prognosis anyway.

The site of metastases and their frequency has been well documented by Merriam (1950), Carbajal (1959), Taktikos (1966), and Wintersteiner in Duke-Elder (1967). Merriam (1950) in his analysis of 17 necropsies reported that retinoblastoma was by no means a purely local and cranial disease. In his series 8 patients (47%) died with disease confined to the head and/or spinal cord. The other 9 patients (53%) had distant metastases in addition to those present within the skull. This observation was confirmed by the 24 cases he collected from the literature in which the figures were 45·8% and 54·2% respectively. Carbajal (1959) found a higher incidence of intracranial and spinal spread (75%), and conversely Taktikos (1966) found that spread was more frequently by way of the blood stream, only 29% having CNS involvement. In the present series the disease was confined to the intracranial contents, structures of the orbit, or spinal cord in 12 patients

(48%). There were distant metastases in 13 patients (52%).

Merriam (1950) found that the choroid was involved in all cases with haematogenous metastases. Leber in Merriam (1950) agreed that the most logical and frequent site of vascular invasion was the choroid, and Wintersteiner and Nattini in Merriam (1950) proved that cells grow in the thin-walled choroidal vessels. Carbajal (1959) and Taktikos (1966) both had cases in which choroidal invasion alone must have been responsible for haematogenous dissemination. In this series there are only 2 cases (C2, N3; C2, N1) with haematogenous metastases, where the full thickness of the choroid was involved, without penetration of the sclera. In all the other patients with haematogenous metastases (11), although the choroid was involved the tumour had extended either into or through the sclera and probably involved the iris in 8 cases. None of the remaining 22 patients with choroidal invasion alone developed haematogenous metastases despite full-thickness invasion in 11 cases.

The site of metastases in relation to optic nerve and scleral/extrascleral extension is not clear-cut. The C2, N3 patient mentioned above died of haematogenous metastases. Another patient (N1, C4*b*) developed CNS as well as haematogenous metastases. There is a greater proportion of CNS to distant metastases in both N3 (87·5% : 50%) and C3 and 4 groups (71% : 52%), although the proportion is less in the latter group. The percentage of local disease is greater in the C3 and 4 groups than in the N3 group (81% and 62·5%). Once the disease has passed the N2, C2 stage the risk of developing metastases at either site or recurrent local disease is greatly increased.

Table 10 compares the various systems which are used to stage retinoblastoma. The system of Reese and Ellsworth (1963) is a clinical staging based on the findings in the eye, and prognosis for vision is related to the various stages. To this Bedford *et al.* (1971) had added group VI, which includes extra-ocular extension of the tumour through either the nerve or sclera. The systems of McKenzie in Zimmerman (1961), Carbajal (1958), and Brown (1966) are histological classifications of the nerve and choroid separately. We feel that the Cape Town staging embraces the whole spectrum of the disease and can be used as a guide to prognosis and treatment.

Stage I includes those lesions amenable to local therapy—Reese and Ellsworth's (1963) groups I to IV. In a recent article Merriam (1978) advised enucleation in group V, and this would therefore be included in the Cape Town stage II. While agreeing with Reese and Ellsworth's classification in principle, we should mention that site is an important factor as well as size. A small lesion overlying the optic disc, fully or partially, can be treated only with external beam therapy, and if there is any doubt as to its complete regression enucleation is indicated. Aherne and Roberts (1975) found that there was a poor prognosis with tumours at this site. A small lesion situated anywhere other than the optic disc or macula is readily accessible to an I^{125} radioactive plaque (Sealy, 1977), and therefore anterior lesions do not necessarily carry the poor prognosis originally ascribed to them. Reese and Ellsworth (1964) noted that with more thorough examination of the ora serrata and by using means other than external beam therapy, which probably missed these lesions while they were trying to spare the lens, anterior lesions had a more favourable prognosis.

Stage II is a histological staging of those lesions unsuitable for conservative local therapy but still ostensibly confined to the eye and orbit. The substages of stage II can offer a fairly reliable prognosis for survival and a guide to the essential modality of treatment, whether external irradiation or chemotherapy, or both. In substages N0, N1, C0, C1 no further treatment is required and the prognosis for life is excellent. Substages N2 and C2 require additional therapy to enucleation and the prognosis is still very good. The prognosis becomes considerably worse in substages N3, C3, and C4, and it is these stages which require recognition and aggressive prophylactic therapy if a cure is to be obtained.

In stage III the lesion has spread beyond the orbit but has not undergone haematogenous spread. This may be detected clinically or by cytological examination of the CSF, brain scan, and computerised axial tomographic scan.

In stage IV haematogenous spread has occurred and may be detected clinically or by skeletal survey, bone scan, and examination of the bone marrow together with a trephine biopsy.

It can be seen that accurate staging of retinoblastoma patients, clinically, histologically, and with the tests that are available, not only gives a reliable prognosis but provides a guide to the minimum necessary effective treatment, an important factor in growing children, and offers more hope for those patients in stage II N3, C3, or C4, if the seriousness of their disease is appreciated and prophylactic treatment instituted. The design of treatment related to this staging will be subject to a further communication.

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Table 10 *Comparison of present systems of staging retinoblastoma*

Cape Town		*Reese and Ellsworth (1963)*	*Bedford* et al. *(1971)*
Stage I. Lesions amenable to local therapy		Group I (*a*) Solitary tumour less than 4 dd in size; (*b*) Multiple tumours none over 4 dd in size — at or behind the equator Group II (*a*) Solitary lesion 4 to 10 dd in size; (*b*) Multiple tumours 4 to 10 dd in size — behind the equator Group III (*a*) Any tumour anterior to the equator (*b*) Solitary tumour larger than 10 dd behind the equator Group IV (*a*) Multiple tumours, some larger than 10 dd (*b*) Any lesion extending anterior to the ora serrata	Group I–V as Reese and Ellsworth
Stage II. Lesions unsuitable for conservative local therapy, but still ostensibly confined to the eye and orbit		Group V (*a*) Massive tumours involving over half the retina (*b*) Vitreous seeding	
Nerve	*Choroid*		
N0 No invasion	C0 No invasion		
N1 Invasion up to or in lamina cribrosa	C1 Involvement of superficial layers of choroid up to half its thickness		
N2 Invasion beyond lamina cribrosa. Resection line free			
	C2 Full thickness of choroid		
N3 Nerve involved up to resection line			Group VI. Optic nerve involvement
	C3 Scleral involvement (*a*) ± ciliary body (*b*) Ciliary body, iris and anterior chamber involved		
	C4 Extra-scleral involvement (*a*) ± ciliary body (*b*) Ciliary body, iris and anterior chamber (*c*) Total destruction of eye by tumour		Extra-scleral extension Residual orbital disease
Stage III. Lesions which have spread beyond the orbit but not yet undergone haematogenous metastases G1 Pre-auricular node G2 Other nodes B1 Positive brain scan or malignant cells in CSF. No clinical sign of disease B2 Clinical malignant meningitis B3 Relapsing intracranial disease			
Stage IV. Lesions which have undergone haematogenous metastases M1 Bone marrow M2 Clinical or radiological bone involvement M3 Liver M4 Multiple organs involved			

McKenzie in Zimmerman (1961)		*Carbajal (1958)*		*Brown (1966)*	
Nerve	*Choroid*	*Nerve*	*Choroid*	*Nerve*	*Choroid*
Stage 0 **No invasion**	None	No involvement		I. Not involved	No involvement Grade 0. Tumour internal to pigment epithelium Grade 00. Tumour external to pigment epithelium
Stage I. Anterior to but not beyond lamina cribrosa	Slight	Anterior-optic cup anterior to lamina cribrosa	**Grade I.** Confined to choriocapillaris **Grade II.** Invasion of large vessels but not entire thickness	II. Nerve involved (*A*) Anterior to lamina cribrosa 1. Optic cup 2. Anterior to or including lamina cribrosa	Grade I Grade II
Stage II. Beyond lamina cribrosa but not as far as resection line		Posterior Nerve axis only		(*B*) Posterior to lamina cribrosa 1. Nerve axis only	As Carbajal
	Moderate to to marked	Vaginal sheath only	**Grade III.** Entire choroidal layers	2. Vaginal sheath only (*D*) Cells do not cross line of transection	Grade III Grade IV Only supra-choroidal space involved
Stage III. Involvement at plane of surgical transection		Both nerve axis and vaginal sheath		3. Both nerve axis and vaginal sheath (*C*) Cells do cross line of transection	
			Scleral involvement		Scleral involvement
					Epibulbar involvement

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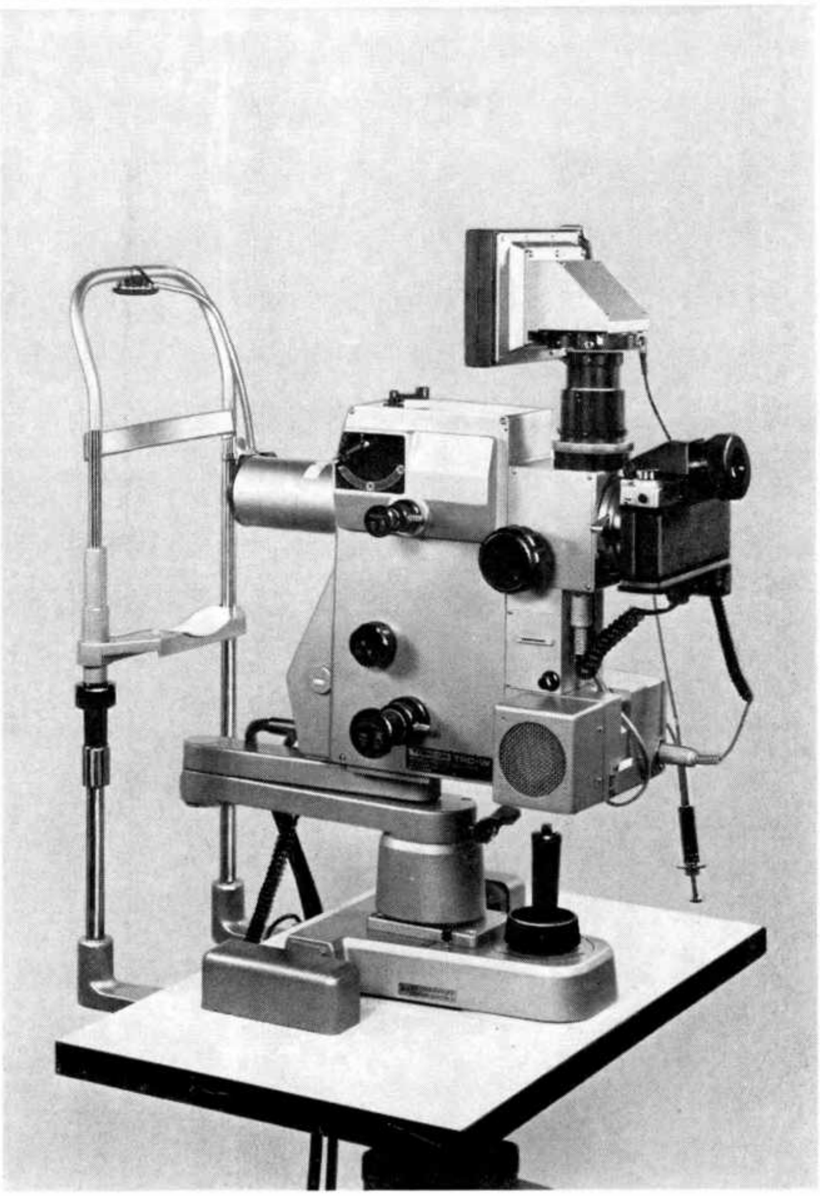

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Prognostic significance of aqueous humour lactic dehydrogenase activity

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SUMMARY The lactic dehydrogenase (LDH) activity of the aqueous humour has been estimated in both eyes of 7 patients having uniocular retinoblastoma. In 1 patient the aqueous humour LDH activity in the healthy eye was above normal, but there was no clinical evidence of malignancy. Tumour tissue was detected in this eye 9 months later, and the aqueous humour showed a rise in LDH activity. A high LDH activity persisted even after irradiation, though no tumour tissue was visible ophthalmoscopically. It is suggested that the estimation of the LDH activity in the aqueous humour of the healthy eye in cases of uniocular retinoblastoma might be of value in the early detection of a bilateral retinoblastoma.

The diagnostic significance of an increase in the lactic dehydrogenase (LDH) activity in the aqueous humour was first demonstrated by Dias *et al.* (1971). Since then several other workers have confirmed these findings (Kaneko and Suzuki, 1972; Swartz *et al.*, 1974; Kabak and Romano, 1975; Felberg *et al.*, 1977). An increased LDH activity, however, has also been reported in other nonmalignant conditions associated with intraocular cell necrosis (Stone and Krupin, 1976). There is no doubt that, together with other ancillary investigations, the estimation of LDH activity in the aqueous humour is an invaluable procedure in the diagnosis of retinoblastoma.

Since about 25% of the cases of retinoblastoma are bilateral, it was decided to investigate the LDH activity in the aqueous humour of the healthy eye in patients with established unilateral retinoblastoma, to determine whether the estimation of LDH activity would be of help in the early diagnosis of retinoblastoma in the healthy eye.

Materials and methods

Aqueous humour was collected by aqueous puncture from both eyes of 7 patients who presented at the Victoria Memorial Eye Hospital, Colombo, with a white mass clinically diagnosed as a retinoblastoma behind 1 pupil, the other eye being clinically completely normal. The specimens of aqueous humour were kept at 4°C and analysed the same day.

The LDH activity was estimated by the colorimetric method of King (1959), in which the increase in optical density at 340 nm was measured. A unit of activity is the amount of LDH which reduces 1 μmole lactate to 1 μmole pyruvate in 15 minutes at 37°C. Activity is expressed in units per 100 ml of aqueous humour (SI conversion: units/l = units/100 ml × 10). Care was taken to see that none of these specimens was contaminated with blood.

Results

The LDH activity of the aqueous humour in the 7 eyes containing the white mass ranged between 1460 and 3400 units/100 ml, and were all considered to be in the malignant range (values over 1000 units/100 ml were regarded as being malignant [Dias *et al.*, 1971]). These eyes were all enucleated, and subsequent histology showed a retinoblastoma in each case.

The aqueous humour removed from the healthy eyes of 6 of these 7 patients ranged between 180 and 420 units/100 ml. The normal range is 160 to 400 units/100 ml (King, 1959). In 1 of these patients with unilateral retinoblastoma, however, the aqueous humour removed from the healthy eye showed an LDH activity of 840 units/100 ml. This level, though above the normal range, was below the range considered to be malignant. The case history of this child is recorded below.

CASE REPORT

A girl aged 1½ years was brought to the Eye Hospital,

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Colombo, in May 1977 with a history of a white mass behind the left pupil of 6 weeks' duration. The pupil was dilated and fixed. The tension was increased, the anterior chamber was deep, and the iris showed atrophic patches. Floccules of necrotic material were present in the vitreous, and the retina was completely infiltrated by a yellowish white vascular mass producing a solid retinal detachment. Clinically the right eye was perfectly normal, and there was no traceable family history of retinoblastoma.

A diagnostic aqueous puncture done on the left eye revealed an LDH activity of 2360 units/100 ml, confirming that the mass was most likely to be a retinoblastoma. The eye was enucleated, and at the time of enucleation aqueous humour was removed from the clinically normal right eye for LDH assay. The LDH activity of the aqueous humour in the right eye was 840 units/100 ml, and histological examination of the left eye showed an undifferentiated retinoblastoma with areas of necrosis and calcification but showing no invasion of the optic nerve or choroid.

The child was discharged from hospital in July 1977, but through default was followed up very irregularly. In February 1978 it was observed that there was a small yellowish mass near the posterior pole with a well-defined temporal edge. A diagnostic aqueous puncture was performed, and the LDH activity of the aqeuous humour at this stage was 1170 units/100 ml. The child was given external cobalt therapy of 3500 rads over 4 weeks to the right eye. (Cobalt plagues are not available in Sri Lanka.)

In May 1978 examination of the right eye revealed no trace of the mass at the posterior pole, and an estimation of the LDH activity in this eye showed it to be 760 units/100 ml.

Discussion

The initial LDH estimation in the clinically normal right eye, which was of a value higher than normal, probably suggests the presence of a tumour which was too small to be seen ophthalmoscopically but which was actively secreting LDH. It is known that malignant cells are capable of actively secreting LDH into the surrounding body fluids (Wroblewski, 1957). The increase in the LDH activity of the aqueous humour in this eye during a period of 9 months leaves no doubt as to the occurrence of a malignant tumour in the right eye.

The reason for the subsequent persistence of the LDH activity of the aqueous humour in the right eye at a level higher than normal even 2 months after irradiation is difficult to explain. It is probably due to the lysis of cells caused by irradiation and the release of intracellular LDH, which, being globulin in nature, is only slowly removed from the aqueous humour; or it could indicate the persistence of remnants of tumour tissue too small to be seen ophthalmoscopically but still actively secreting LDH.

It is well known that the serum creatine phosphokinase (CPK) levels are very high in children who have the Duchenne type of muscular dystrophy. These enzyme levels are very high in children predisposed to dystrophy even at birth, long before any signs or symptoms of dystrophy are clinically detectable (Smith *et al.*, 1966). Raised enzyme levels in asymptomatic children having a family history of dystrophy are therefore of diagnostic significance. Abnormal carcinoembryonic antigen levels have been demonstrated in family members of cases of retinoblastoma showing no clinical or ophthalmoscopic manifestations (Felberg *et al.*, 1976).

Since retinoblastomas are associated with a very high LDH activity, it is likely that the LDH activity in the aqueous humour of the healthy eye would be raised in the very early stages of a case of retinoblastoma, even before the tumour mass is visible ophthalmoscopically. It is suggested that the LDH activity be routinely estimated in the healthy eye of patients having unilateral retinoblastoma even though the healthy eye may appear clinically and ophthalmoscopically normal, for this may help in the early detection of a bilateral retinoblastoma and thus greatly improve the prognosis through early treatment. There could possibly even be a place in the future for 'prophylactic radiotherapy' to the healthy eye in patients with unilateral retinoblastoma who show a raised LDH activity in the healthy eye even without any clinical or ophthalmoscopic manifestations.

I thank the surgeons at the Victoria Memorial Eye Hospital, Colombo, who extended to me their fullest co-operation, and Miss Cheryl Fernando for secretarial assistance.

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Correlation of aqueous humour lactic acid dehydrogenase activity with intraocular pathology

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SUMMARY An analysis of the lactic acid dehydrogenase (LDH) activity in the aqueous humour of 24 enucleated eyes with retinoblastoma showed that though there was no relationship between the LDH levels and the age of the patient, there appeared to be an increase in the LDH activity with increase in the duration of the tumour. Undifferentiated tumour cells and tumour cell necrosis seemed to contribute to an increase of LDH levels in the aqueous humour, but there was no relationship between the occurrence of calcification and the LDH secretion into the aqueous humour. Massive cell necrosis caused by radiotherapy and central retinal artery occlusion significantly increased the LDH levels in the aqueous. It also appeared that recurrence was common after external cobalt therapy and that secondary extension of the tumour into the optic nerve and choroid was favoured by this procedure.

Although an increase in the lactic acid dehydrogenase (LDH) activity in the aqueous humour has been reported in non-malignant intraocular conditions associated with cell necrosis (Stone and Krupin, 1976) there appears to be no doubt that, together with other ancillary investigations, the estimation of LDH activity in the aqueous humour is an invaluable procedure in the diagnosis of retinoblastoma (Dias *et al.*, 1971; Kaneko and Suzuki, 1972; Swartz *et al.*, 1974; Kabak and Romano, 1975; Felberg *et al.*, 1977).

The purpose of this study was to correlate the aqueous humour LDH activity with intraocular pathology to determine whether factors like secondary spread of the tumour, duration of the tumour, age of onset, radiotherapy, and tumour pathology could influence the LDH activity.

Materials and methods

Aqueous humour was collected by aqueous puncture from 25 patients who presented at the Victoria Memorial Eye Hospital, Colombo, for enucleation of 1 of their eyes. These specimens were kept at 4°C and analysed the same day.

LDH activity was estimated by the colorimetric method of King (1959), in which the increase in optical density at 340 nm was measured. A unit of activity is the amount of LDH which reduces 1 μmol lactate to 1 μmol pyruvate in 15 minutes at 37°C. Activity is expressed in units/100 ml of aqueous humour (SI conversion: units/l = units/100 ml × 10). Care was taken to see that none of these specimens was contaminated with blood.

The enucleated eye was fixed in formol saline, and the paraffin sections were stained with haemotoxylin and eosin. Ten sections containing the tumour were examined from each eye.

Twenty-four of these patients presented with a white mass behind the pupil and were diagnosed preoperatively on clinical grounds as having a retinoblastoma. Subsequent histology showed a retinoblastoma in each case. One patient, however, had a non-malignant intraocular condition associated with a raised LDH level in the aqueous humour.

Results

DURATION OF THE TUMOUR

It was difficult to obtain an accurate assessment of the exact duration of the tumour. The only indication was the duration of time since it was first noticed by one or other parent. Both parents were closely questioned independently to obtain an idea of its duration. The relationship between the duration of the tumour as estimated in this manner and the LDH activity is presented (Table 1).

The 3 patients in whom the duration of the tumour was more than 6 months were clinically diagnosed as retinoblastoma and confirmed by LDH

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Table 1 *Relationship between the duration of the tumour and aqueous humour LDH activity*

Duration (months)	*Number of patients*	*LDH activity in aqueous humour (units/100 ml)*	
		Mean	*Range*
Less than 1	6	1927	1220–2660
1–3	11	2272	1890–2660
4–6	4	2700	2480–2840
7–12	2	3555	3460–3650
More than 12	1	3850	—

Table 2 *Relationship between radiotherapy and aqueous humour LDH activity*

Age of child when first seen	*Initial LDH activity (units/100 ml)*	*Duration since radiotherapy (months)*	*LDH activity (units/100 ml) on enculeation*
1 year 2 months	2120	9½	3460
2 years 7 months	2860	16½	3850
4 years 3 months	1800	10	3650

Table 3 *Relationship between age of child and aqueous humour LDH activity*

Age of child (years)	*Number of children*	*LDH activity in aqueous humour (units/100 ml)*	
		Mean	*Range*
Less than 1	4	2675	2580–2820
1–3	11	2280	1640–2860
4–5	8	2014	1220–2660
Over 5	1	2240	—

assay (Table 2). They were advised enucleation but the parents refused and preferrerred to have the eyes irradiated. All 3 of them presented at a later date for enucleation and the LDH values prior to enucleation are shown in Table 1.

AGE OF ONSET

Though classically retinoblastoma is a tumour of infancy, in this series it tended to occur more frequently in a slightly older age group (Table 3).

One child in this series was a girl of 9 years, and doubt existed whether this could be an endophthalmitis or a case of Coats's disease. A diagnostic aqueous puncture revealed an LDH activity of 2240 units/100 ml, indicating that the mass was most likely to be a retinoblastoma. The eye was enucleated, and histological examination showed an undifferentiated retinoblastoma containing areas of necrosis and calcification with no invasion of the choroid or optic nerve. Retinoblastoma, when it occurs in the older age group, usually appears as a flat diffuse type of growth, being more like a thickened retina. The exophytum type of growth as was seen in this patient is not a common feature in the older age group.

TUMOUR PATHOLOGY

All 24 eyes examined showed necrotic areas within the tumour mass and all of them were poorly differentiated retinoblastoma. Areas of calcification, however, were seen only in 14 patients. None of the patients in whom the duration of the tumour was less than 1 month showed calcification.

There was no correlation either between the occurrence of calcification and the LDH activity of the aqueous humour or between the occurrence of calcification and the age of the patient.

EFFECT OF RADIOTHERAPY

In this series 3 patients had received radiotherapy prior to enucleation. They were all clinically diagnosed initially as cases of retinoblastoma and confirmed by aqueous humour LDH assay (Table 3). They were all given external cobalt therapy, 3500 to 4000 rad over 4 weeks (cobalt plaques are not available in Sri Lanka).

All 3 children returned to the Eye Hospital, Colombo, within 1½ years with a proptosed eye which needed enucleation. LDH activity at the time of enucleation was recorded (Table 2). Histology showed an undifferentiated retinoblastoma in each case with secondary extension into the optic nerve and choroid.

EXTRAOCULAR SPREAD

Four eyes in this series showed on histological examination an extraocular extension into the optic nerve and choroid. Three of these patients had previously received radiotherapy, and their LDH activity in the aqueous humour just prior to enucleation was 3850, 3650, and 3460 units/100 ml.

The other patient, who had not received radiotherapy but who had an extension into the optic nerve, showed an LDH activity of 2660 units/100 ml at the time of enucleation. In all patients the tumour had persisted for more than 5 months.

The case history of the patient who had a non-malignant intraocular condition with increased LDH activity in the aqueous humour is recorded below.

Case report

A 47-year-old man presented with blindness and pain of sudden onset in the left eye of 3 weeks' duration. Visual acuity was RE, 6/6; LE, NPL. The left eye showed a chemosis of the bulbar conjunctiva and the pupil was dilated and fixed. The anterior chamber in the right eye was shallow. Slit-lamp examination revealed the presence of cells, and there was a visible flare. Keratic precipitates were also seen. Funduscopic examination showed optic atrophy in the left eye. This was a clear-cut case of left central retinal artery occlusion with acute uveitis. Further investigations revealed an absent right radial pulse and an absence of both carotid pulsations. Archangiogram revealed a complete occlusion of the innominate artery and the upper part of the right internal carotid artery. There was a large amount of atheromatous change in the aorta which was probably the source of the embolic changes in the left eye.

The case was diagnosed as one of aortic arch syndrome, and the left eye was enucleated. Just prior to enucleation aqueous humour was removed for LDH assay.

The LDH level was abnormally high—1075 units/100 ml—and was in the range of intraocular malignancy (aqueous humour LDH levels of over 1000 units/100 ml are regarded as being suggestive of intraocular malignancy (Dias *et al.*, 1971)).

Histological examination of the enucleated eye showed a haemorrhage at the disc and in the posterior part of the vitreous, with no abnormality in the anterior segment, but there was no tumour tissue in the eye.

Discussion

The correlation of the LDH activity in the aqueous humour with the duration of the tumour as assessed by the time since it was first noticed by the parents appears to indicate that the longer the duration of the tumour, the higher was the LDH activity in the aqueous humour. This could probably be attributed to the growth of the tumour and the resultant increase in the number of LDH-secreting malignant cells. Further, the growth of the tumour promotes necrosis of cells within the tumour mass, which increases the release of intracellular enzymes into the aqueous humour.

The 3 eyes in which the tumour had persisted for more than 6 months were from patients who had received radiotherapy, but the effect of radiotherapy as being the cause of an increase in LDH activity could be eliminated, because they had all received radiotherapy at least 9 months previously.

The age of onset of the tumour had little or no bearing on the LDH activity in the aqueous humour.

Of the 4 patients who showed retro-ocular spread of the tumour 3 had received radiotherapy, and they had very high LDH levels in the aqueous. In fact the highest LDH levels recorded in this series were in 3 patients who presented with a recurrence of the tumour after radiotherapy. The other patient who had not received radiotherapy but who also showed retro-ocular spread had a relatively lower LDH level in the aqueous. It appears that retro-ocular extension by itself is unlikely to cause a gross elevation of the LDH activity. It would have been interesting to estimate the LDH activity in the cerebrospinal fluid of these patients who showed a secondary spread into the optic nerve, but unfortunately this could not be done in any of them.

As cobalt discs are not available in Sri Lanka, external cobalt therapy is the method of radiotherapy for retinoblastoma. Though retinoblastoma is far more radiosensitive than melanoma, statistics are not available in Sri Lanka for the 5-year survival rate after irradiation by this method.

In the present series 3 patients were given the full dose of radiotherapy, but in all 3 the tumour recurred within 1½ years, resulting in enucleation, and all 3 patients showed very high LDH levels in the aqueous with retro-ocular extension into the optic nerve and choroid. Radiotherapy appears to promote the retro-ocular spread of the tumour, probably on account of damage to the tissues in the posterior part of the eye, with resulting spread of the tumour.

Regarding recurrence of the tumour and retro-ocular spread following radiotherapy, a larger series and a long-term follow-up are essential to determine whether external cobalt therapy as it is administered today in Sri Lanka is of any significant value in the treatment of retinoblastoma, because the possibility exists that radiotherapy could in some way favour the spread of the tumour into the choroid and optic nerve.

Since all specimens examined showed areas of tumour necrosis, it was difficult to assess to what extent tumour necrosis contributed to the elevated LDH activity. Similarly, it was difficult to assess to what extent the degree of differentiation of the tumour affected the LDH activity in the aqueous humour. It seems that, though the bulk of the enzyme is actively secreted by poorly differentiated malignant cells (Wroblewski, 1957), intracellular enzyme release due to lysis of cells resulting from tumour cell necrosis may also contribute to the total LDH activity in the aqueous humour.

There was no relationship between the occurrence of calcification in the tumour mass and the LDH activity in the aqeous humour.

The fact that LDH levels could be elevated in the aqueous humour even in non-malignant intraocular conditions which cause cell necrosis is illustrated by the patient with a central retinal artery occlusion.

As enzymes and metabolites from the retinal network could pass forwards by diffusion through the vitreous into the aqueous (Dias and Amarasiri, 1978) infarction of the retina could increase the LDH activity of the aqueous humour in the absence of intraocular malignancy.

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Surgical management of carcinoma of eyelids and periorbital skin

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SUMMARY An appraisal of a personal series of 115 unselected and surgically treated cutaneous cancers of palpebral region is presented. Histological confirmation of the diagnosis and adequacy of excision was obtained for all lesions. Seven of the 8 patients with doubtful clearance were successfully treated with further surgery very soon. Complications were few, the incidence of re-operations low, and cosmetic as well as functional results were mostly satisfactory. Tumour recurred in 1 case (0·87%). Two patients had a poor cosmetic result. Seventy-nine cases (69%) were treated as day cases under local anaesthesia even for major repairs like full-thickness reconstruction of two-thirds of the lower eyelid and repairs with large full-thickness skin grafts of up to 20×55 mm by a new simple technique of graft fixation. The use of longer-acting local anaesthetics in oculoplastic surgery is described. Attention is drawn to the dangers of using direct wound closure for repair.

Apart from the readily observable cosmetic blemish that they produce malignant tumours of the skin of the eyelids and periorbita differ from cutaneous malignancies elsewhere by their tendency to damage the ocular and adnexal structures either by direct invasion or as a consequence of therapy. Whatever the method employed to treat such lesions, the objectives should therefore be the eradication of the tumour in toto, without any damage or potentiality of damage to the structure and function of the eye and its adnexa, and the ultimate attainment of a normal or near normal functional and cosmetic result. Only rarely is it impossible to achieve such desirable results by primary surgery in experienced hands. The aim of this communication is to analyse the clinical features and results of 115 epithelial carcinomata surgically treated by the author personally in an ophthalmic unit.

Patients and methods

One hundred and forty-three unselected patients with 154 malignant or suspected malignant lesions of the eyelids and periorbita were treated by excision and surgical repair in the author's unit between January 1969 and December 1977. Of these 6 were recurrences following primary treatment elsewhere—2 by radiotherapy and 4 by surgery, including a rodent ulcer that was curetted elsewhere, having been mistaken for a meibomian cyst. All excised lesions were examined histologically for confirmation of diagnosis and completeness of excision. Those patients reported as having inadequate or doubtful clearance were soon operated on again to obtain histological confirmation of the adequacy of tumour excision.

Eight such patients have not been included in the statistics of recurrence. During these 9 years 1 patient was referred from the unit for primary radiotherapy. The patient was averse to surgery and had basal cell carcinoma on the side of the nose extending to the lacrimal sac region. During the same period 7 patients with rodent ulcers of the eyelids were referred by radiotherapists to the unit for primary surgery. The remaining patients were referred by general practitioners, dermatologists, ENT surgeons, and ophthalmic and general surgical colleagues.

Of the 154 lesions treated surgically in this series 115 were malignant tumours—109 basal cell carcinomata, 4 squamous cell neoplasms, 1 melanoma, and 1 Bowen's disease. To simplify statistical analysis each multiple lesion in the same patient has been counted as an additional case. Detailed analysis of only the 109 basal cell lesions has been done, as the incidence of other tumours was very small. The incidence of rodent ulcers was slightly

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more in males (58 cases) than in females (51 cases). The youngest patient was 31 years old, and the oldest was 93. The age distribution is shown in Table 1.

The topographical distribution of the tumour is depicted in Table 2. The lower eyelid was the commonest site affected. The eyelid margin was involved in 40 cases. Lesions situated medial to the lacrimal punctum, or on the eyelid but extending medial to the punctum, have for statistical purposes been accepted as inner canthus lesions. Similarly, any lesion situated on the upper or lower eyelid but extending to the external canthus has been classified as a lateral canthus lesion.

As the size of the tumour was not recorded in all cases, the magnitude of excision—taken as the maximum dimension reported as 'macroscopic appearance' in the histopathology reports—is summarised in Table 3. The smallest excision was 9×10 mm, and the largest was 20×55 mm. Except for 5 patients who are lost to follow-up and 29 who have died of unrelated conditions, all patients continue to have regular follow-up. The maximum follow-up period has been 9 years and the minimum 11 months. A follow-up of 18 months or more was achieved in 93·2% of the patients (average 3·7 years).

Table 1 *Age of the patients at initial excision of the rodent ulcer (the youngest patient was 31 and the oldest 93)*

Age in years	*Number of patients*
Under 31	Nil
31–	3
41–	4
51–	25
61–	42
71–	29
81–	4
91–100	2
Total	109

Average age 65·6 years

Table 2 *Topographical distribution of the rodent ulcers (40/109 tumours involved lid margins)*

Location of tumour	*Number of cases*
Lower eyelid	59
Inner canthus	28
Upper eyelid	13
Outer canthus	9
Total	109

Table 3 *Magnitude of tumour excision (longest diameter) (smallest excision 9 mm, largest excision 55 mm)*

Excision in mm	*Number of cases*
8–10	7
11–15	26
16–20	58
Over 20	18
Total	109

SURGICAL MANAGEMENT

Except for a few lesions in the earliest part of the series all tumours were excised with at least 4 mm clinical clearance. Following the precept of Whiting (1951) in judging the clearance, the visual as well as the tactile impression with ungloved fingers was utilised. With progressive surgical experience the excisions have tended to be increasingly liberal. Pre-excisional biopsy was carried out only on those patients in whom suspiciously malignant-looking lesions were situated at or near the eyelid margins. In such cases wider excision and full-thickness eyelid repair were carried out only if the histology proved the lesion to be malignant. A frozen-section report was obtained in only 1 patient, who had an extensive rodent ulcer at the inner canthus involving the upper and lower eyelids. It confirmed the clinical suspicion of invasion of the bulbar conjunctiva, thereby facilitating the decision to carry out enucleation and 'hemiexenteration' (see below).

ANAESTHESIA AND GENERAL MANAGEMENT

General anaesthesia was used for the first 31 cases of this series. These patients were admitted to the hospital. The remaining 84 patients with malignant lesions (and 39 patients with suspected malignant lesions) received local anaesthesia and were treated as day cases, except for 5 patients who were admitted to the hospital for social reasons. As the local anaesthetic effect of lignocaine tended to wear off in about an hour or so, all patients except the initial few operated upon under local anaesthesia received local infiltration of 2 ml bupivacaine 0·5% with adrenaline (Marcain). Those patients requiring full-thickness eyelid reconstruction were in addition given *retrobulbar injection* of 2 ml Marcain, and a *facial nerve block* also with 2 ml Marcain. The donor site for obtaining full-thickness skin graft (and that for a mucous membrane graft if necessary) was also infiltrated with 2 to 4 ml Marcain. The

Table 4 *Surgical procedures used for 115 cases of cutaneous malignancies in the peripalpebral region*

Site of lesion	*Method of repair*	*Number of cases*
1. Lesions not involving eyelid margin; situated more than 5 mm from the margin; situated on upper or lower eyelid, or at nasocanthal angle	(*i*) Full-thickness skin graft. Technique in most cases (Mehta, 1977, 1978), Fig. 1	71
	(*ii*) Pedicle flap from the adjacent upper eyelid skin	2
2. Lesions involving full-thickness lower eyelid or situated within 5 mm of its margin	(*i*) Full-thickness skin graft with simultaneous free mucosal graft (Mehta, 1977)	17
	(*ii*) Free mucosal graft with local rotational flap or canthoplasty (Mustardé, 1966)	13
	(*iii*) Tarsoconjunctival flap from upper eyelid (Holström *et al.*, 1975; Hewes *et al.*, 1976) with simultaneous full-thickness skin graft by the author's technique	4
3. Lesion involving full-thickness upper eyelid or situated within 5 mm of its margin	(*i*) Full-thickness rotational flap from lower eyelid (Mustardé, 1966).Later reconstruction of the lower eyelid as in 2 (*i*) above	3
4. Miscellaneous—especially lesions at inner canthus	(*i*) Wide excision allowing repair by spontaneous granulation (Beard and Fox, 1964)	4
	(*ii*) Enucleation and 'hemiexenteration', Fig. 5	1
Total		115

prolonged local anaesthetic effect of a single infiltration with bupivacaine made it possible to perform extensive procedures like subtotal full-thickness reconstruction of eyelids (lasting for 3¼ hours) without any additional infiltration. All patients were allowed full activity immediately after the operation. The day cases were seen for first dressing at 48 hours and then between the 7th and 10th postoperative day for removal of sutures. All patients were given 2 co-trimoxazole (Septrin) tablets twice daily for 5 days.

The surgical techniques used to treat the lesions are summarised in Table 4.

Results and comments

Of the 154 lesions submitted for histology a *definite* clinical diagnosis of malignancy was made in 139 lesions and a *tentative* diagnosis in 15 lesions. Histology confirmed malignancy in 114/139 (82%) and 1/15 (6·7%) respectively. In 8 cases histology reports suggested incomplete or doubtful clearance. Seven of these 8 cases were therefore soon subjected to further wide excision. None of the resubmitted specimen showed tumour remnants. It was therefore decided to observe the 8th patient without undertaking further surgery. No clinical evidence of tumour persistence or recurrence has been found in an 18 months follow-up of this patient.

There has been 1 true recurrence (0·87%) of a lower eyelid rodent ulcer that was initially situated 3 mm from the eyelid margin. Histology of the first specimen did confirm complete excision, but 10 months later there was a clinical recurrence, which needed a wide full-thickness excision and repair. The histology of the second specimen confirmed complete clearance. No further recurrence has been found in a 4-year follow-up of this patient. In retrospect, full-thickness excision of the eyelid—because of the proximity of the lesion to the lid margin—should have been carried out at the first operation.

One patient with histologically confirmed complete excision of a rodent ulcer at the inner canthus was clinically suspected of having a recurrence 14 months later. The histology of the second wider excision showed the tumour to be a neurofibroma under the skin graft. One case of multicentric erosive basal cell epithelioma had histological confirmation of adequacy of excision at *each* of the 2 operations. At his last check-up in the unit 2 years ago there was a clinical suspicion of persistence of the tumour. The patient is now being followed-up elsewhere, and the clinicians there do not think there is a recurrence.

There is 1 case of 'permanent failure' in a patient with a deep penetrating rodent ulcer that was already present for 7 years when the patient was first seen. At the time of first wide excision of three-quarters of the lower eyelid in full-thickness the inferior oblique muscle was observed to have been infiltrated with the tumour. The infiltration has become progressively worse, resulting in fixity of the globe. The correct management here should have been exenteration, but the patient refused. Primary enucleation and 'hemiexenteration' (see below) were carried out in 1 patient in whom frozen section confirmed the clinical suspicion of bulbar conjunctiva invasion by a rodent ulcer at the inner canthus. This lesion was already present for 6 years before the patient was first seen. There has been no death due to the tumour in any patient of this series, but 29 patients have died from unrelated conditions during the 9 years of this series. Five patients have been lost to follow-up. The clinical records of these 34 patients show no evidence of tumour recurrence at their last visit.

In the great majority of cases the cosmetic results were gratifying. Skin grafts had merged imperceptibly into the surrounding tissues as regards colour, texture, surface, and suppleness. The eyelids appeared symmetrical, and had normal mobility, providing normal corneal coverage.

COMPLICATIONS

Considering the fact that most of the patients in the series had major reconstructive surgery the incidence of complications was low. No patient had temporary or permanent visual impairment due to the surgery, and apart from the planned enucleation (and hemiexenteration) in 1 case no eyes were lost. None of the patients needed major surgery to combat any of the complications, which were as follows:

Epiphora. This occurred in 11 cases (10%) and varied from tolerable in 9 cases, to annoying in 2 cases. In all the cases the epiphora was due to planned surgical excision that included the lacrimal passages. No patient has needed further surgery for reconstruction of the lacrimal passages.

Trichiasis. It occurred in 4 cases (3·5%) and has been successfully treated with electrolysis.

Minor cosmetic blemishes occurred in 6 patients (5·2 per cent). Three patients had slight ectropion of the lower eyelid. Two had rounding of external canthus, and 1 had mild ptosis. None of these needed corrective surgery.

Healing of full-thickness skin graft by *fibrosis due to haematoma* under the graft occurred in 1 patient in whom the graft was secured by a tie-over bolus technique. Acceptable cosmesis has obviated the need for further surgery.

Poor cosmesis. This occurred in 2 cases (1·7%). Both patients were over 80 years old. One had poor colour match of a full-thickness skin graft after reconstruction of three-quarters of lower eyelid in full thickness by simultaneous buccal mucosal and skin graft. There is sagging of eyelid margin. The second patient had ectropion of the lateral half of lower eyelid. Neither patient opted for further cosmetic surgery.

Complications pertaining to skin graft *donor sites:* (*i*) One patient needed resuturing of a retroauricular wound that gaped on the 6th day. This patient had a previous history of wound gaping in the scapular region. (*ii*) One patient had prolonged non-healing of an inner arm donor site for 10 weeks after removal of a 30×60 mm skin graft. The wound has healed by granulation leaving a prominent symptom-free scar. (*iii*) Temporary difficulty in wearing spectacles for 3 weeks due to tenderness of retroauricular wound occurred in 3 patients.

Discussion

The sine qua non for successful surgery of cutaneous cancers of eyelids is wide excision of the tumour followed by adequate repair of the defect so created. Some of the operations designed to repair these defects are extremely complicated procedures beyond the capacity of most ophthalmologists. The following few relatively simple techniques suitable for adoption by ophthalmic surgeons have therefore been selected for discussion. Some of these techniques have been evolved by the author.

DIRECT WOUND SUTURING

The requisite of wide clearance to ensure success creates a defect so large—even for average lesions—that for a properly excised lesion there is seldom any possibility of repair by direct suturing without risking distortion. Any attempt at minimising the size of the wound to avoid a 'major' repair is likely to lead to an inadequate excision, with increased chances of recurrence of the tumour.

Direct suturing of the wound was not carried out in any of the 115 patients in this series. It is believed that this accounts for the low incidence of recurrence (0·87%) and the low incidence of complications and their relatively minor nature.

FULL-THICKNESS SKIN GRAFTING

This is a very useful procedure for repairing extramarginal wounds as well as achieving full-thickness lower eyelid reconstructions, where it is used in conjunction with a free mucosal graft (Mehta, 1977) or with tarsoconjunctival flaps (Holmström *et al.*, 1975; Hewes *et al.*, 1976). Full-thickness skin grafting is therefore a versatile technique capable of being used for the vast majority of palpebral and peripalpebral tumours. In the present series it was used in 93 out of 115 cases (81%). Of these, 22 were lesions necessitating full-thickness eyelid reconstructions.

The conventional method of securing a full-thickness skin graft by a 'tie-over' bolus has disadvantages, especially of having to restrict the activity of the patients for a few days after the operation. The patients are therefore admitted to

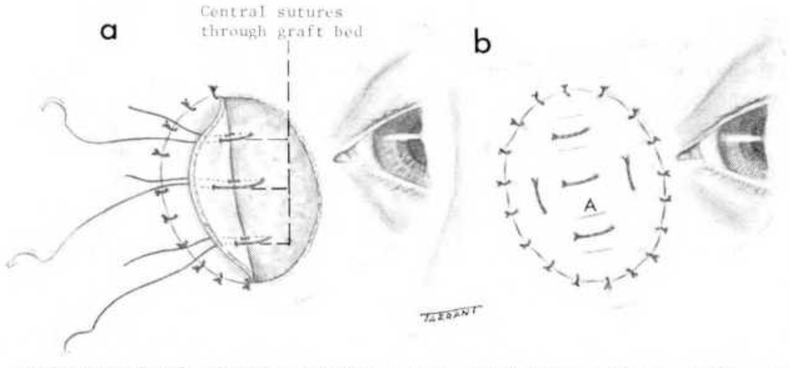

Fig. 1 *Author's technique of full-thickness skin graft fixation. One long edge of the graft is sutured with interrupted marginal sutures of 5–0 polyglycolic acid (Dexon), placed 2 or 3 mm apart. Central and paracentral sutures are now passed between the graft and the depth of the recipient bed. These mattress sutures are tied under moderate tension only after the remaining marginal sutures have been introduced and tied. A tie-over bolus is not necessary. The patients can resume unlimited activity immediately after the operation, as the central sutures will prevent the graft from being lifted off its bed*

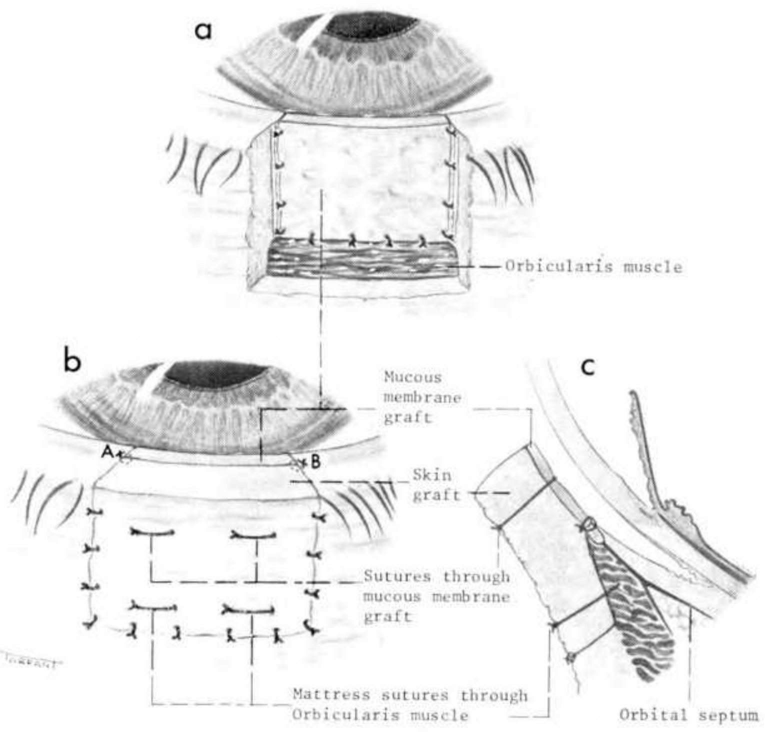
a
Orbicularis muscle
b
c
A
B
Mucous membrane graft
Skin graft
Sutures through mucous membrane graft
Mattress sutures through Orbicularis muscle
Orbital septum

Fig. 2 *Author's technique of full-thickness reconstruction of lower eyelid with simultaneous free mucosal and free full-thickness skin grafts.* (a) *The mucosal graft (nasal septal or buccal) is first sutured to the remaining tarsoconjunctival layer with interrupted marginal 5–0 Dexon sutures with knots tied on the superficial (cutaneous) aspect. The free skin graft is placed over the sutured mucosal graft, and interrupted marginal cutocutaneous (skin graft edge to recipient skin edge) and central cutomucosal mattress sutures, and cutomuscular (skin graft to depth of orbicularis muscle) are introduced and tied as shown in* (b) *and* (c). *Intermarginal sutures between the upper and lower lids may be passed*

hospital. Fox (1976) advocates that the patient be kept in bed for 24 hours, and then allowed only bathroom privileges for the next 48 hours. For a large graft whose take may seem precarious Fox imposes even more stringent restrictions. During the past few years a new technique has been devised (Mehta, 1977, 1979) for full-thickness skin graft fixation, Fig. 1. Over 130 patients have received full-thickness skin grafts secured by this technique. All but 5 of these have been treated as day cases. The largest full-thickness skin graft in the series was 20 × 55 mm. The retroauricular skin is used for small grafts and inner arm skin for grafts larger than 20 mm.

In the full-thickness lower eyelid reconstruction with simultaneous full-thickness skin graft and free buccal mucosa graft (Fig. 2), between the first and third postoperative weeks, the mucosal graft may appear soft, white, and crinkled. This could be alarming both to the patient and to the clinician. But the graft soon resumes normal appearances and the new eyelid margin regains progressive normality in about 8 weeks (Fig. 3). Of the 17 full-thickness lower eyelid reconstructions by the author's method only 1 patient had sagging of the eyelid margin and poor colour match. This was 1 of the 2 patients reported as having had poor cosmesis in this series. For reconstruction of lateral half of the lower eyelid in full-thickness very satisfactory results have been obtained combining the technique of Hewes *et al.* (1976) of tarsoconjunctival rotation with a full-thickness skin graft secured by the author's technique (Fig. 4).

Except for patients who have a tendency to form keloids, there are no contraindications to repair by this technique of skin grafting.

ROTATIONAL PEDICLE FLAP OF FULL-THICKNESS LOWER LID

Mustardé (1966) initiated this excellent technique of reconstructing a full-thickness defect of the upper eyelid. The pedicle is divided in about 2 weeks, when the defect in the lower eyelid is made good.

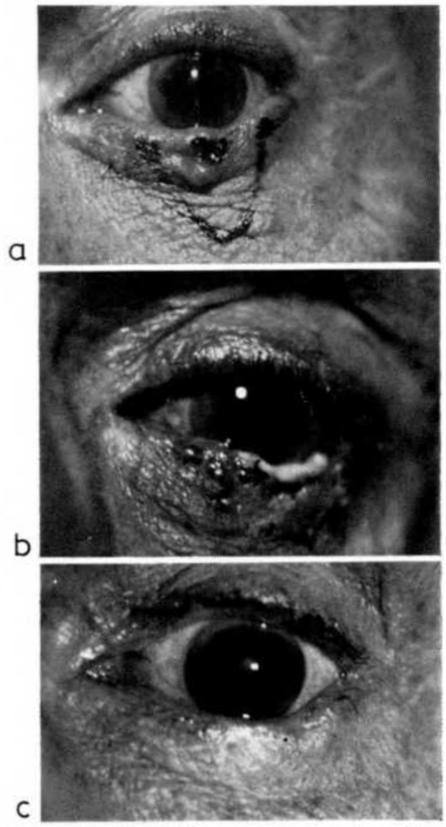

Fig. 3 *Result of full-thickness reconstruction of lower eyelid by technique described in Fig. 2.* (a) *Preoperative appearance of basal cell epithelioma involving eyelid margin.* (b) *Appearance 3 weeks after repair showing healthy skin graft, but soft, white, and crinkled mucosal graft.* (c) *Normal appearance 3 months later*

The results are very satisfying and there are no contraindications for full-thickness upper eyelid reconstruction by this method. Its minor disadvantages are the visual obstruction by the pedicle for 2 weeks and that it needs a second-stage reconstruction of the lower eyelid.

EXENTERATION OR 'HEMIEXENTERATION'

The only patient who needed exenteration in this series has consistently refused it and has been recorded as being a case of 'persistent tumour failure'.

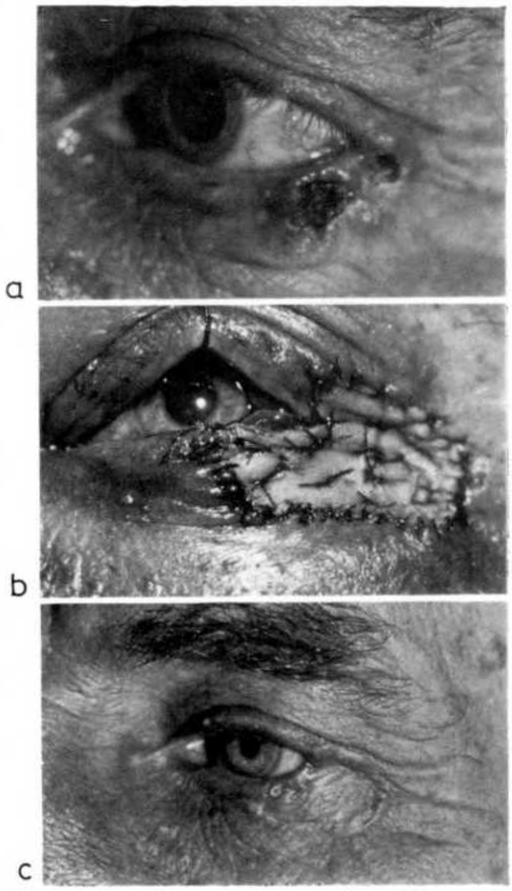

Fig. 4 *Rodent ulcer at the outer canthus. Wide excision included full-thickness lateral half of lower eyelid. Defect made good by tarsoconjunctival transposition from lateral half of upper eyelid, and full-thickness skin graft from inner arm secured by the author's technique shown in Fig. 2. Surgery performed under local anaesthesia as a day case, with the patient resuming his normal work 24 hours after the operation.* (a) *Preoperative appearance.* (b) *Immediate postoperative appearance.* (c) *Appearance 6 months later*

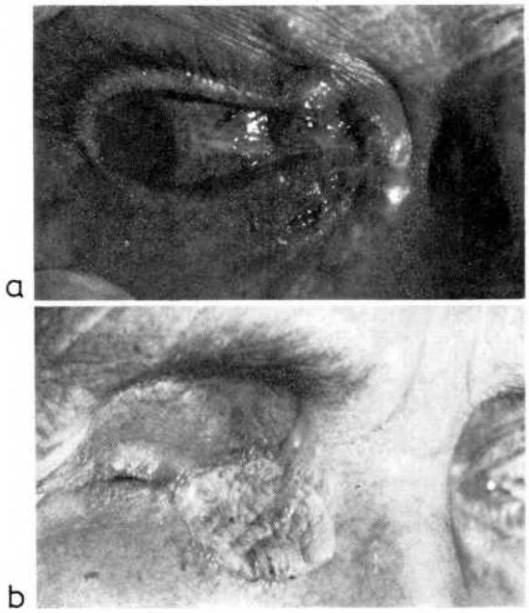

Fig. 5 *Rodent ulcer at inner canthus present for 6 years. At the time of tumour excision clinical suspicion of invasion of bulbar conjunctiva was confirmed by frozen section. The eye was enucleated, and the contents of the medial half of the orbit were exenterated ('hemiexenteration'). Wide excision included full thickness upper and lower eyelid, and medial half of orbicularis muscle. The defect was made good by a full-thickness skin graft secured by central and paracentral sutures to the remnants of conjunctiva, orbicularis, orbital rim, and eyelids. The surgical procedure lasted 4 hours and was performed under local anaesthesia. Originally the patient was scheduled to be treated as a day case, but it was decided to admit her for psychological reasons owing to the unscheduled enucleation carried out after the frozen-section report.* (a) *Preoperative appearance.* (b) *Appearance 3 months after 'hemiexenteration'*

One patient has been managed with 'hemiexenteration'. The clinical suspicion of invasion of bulbar conjunctiva at the inner canthus was confirmed by a frozen section. The medial two-thirds of the upper eyelid and three-quarters of the lower eyelid were both excised in full thickness. The medial half of the orbicularis was excised, the eye was enucleated, and the contents of the *medial half* of the orbit were exenterated. The defect was made good by a full-thickness skin graft of 25×40 mm sutured to the remnants of conjunctiva, orbicularis, eyelids, and the orbital margins by the author's technique. The cosmetic result is very satisfactory (Fig. 5). There has been no recurrence during a 15-month follow-up.

REPAIR BY SPONTANEOUS GRANULATION

Four patients in this series were so managed—after excision of lesions at nasocanthal angle in 2 patients and after excision of full-thickness medial two-fifths of lower eyelid in 2 patients. Three of these patients were elderly, frail, and had cerebrovascular insufficiency. The fourth patient had ugly facial features of gross rhinophyma and numerous other coarse blemishes of the face. Reconstruction of his lower eyelid would have meant merely an academic exercise, striving for perfection that would have looked out of place. The patient himself was delighted to have been offered the choice, and opted to have radical excision (of medial two-fifths of the lower eyelid in full-thickness) without any reconstruction (Fig. 6). The surgery lasted 10 minutes. The cosmetic results in this and other 2 patients

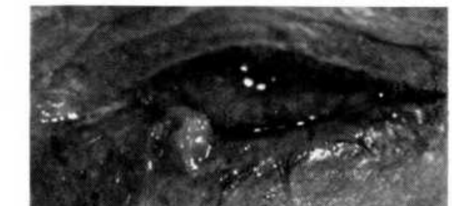

Fig. 6 *Result of healing by spontaneous granulation of full-thickness excision of medial two-fifths of lower eyelid for rodent ulcer involving eyelid margin at inner canthus. The patient having been offered the choice between extensive reconstructive surgery and simple excision without any reconstruction or suturing of the wound opted for the latter procedure, which lasted about 10 minutes.* (a) *Preoperative appearance.* (b) *Immediate postoperative appearance.* (c) *Appearance 3 months later*

were very good. In the fourth patient, who was aged 93, the cosmesis was tolerable. This method of management, first reported by Fox and Beard (1964), deserves wider acceptance in suitable cases as shown above.

The possibility of using the long-acting local anaesthetic Marcain for local infiltration as well as for retrobular and facial block (techniques familiar to all ophthalmologists) allows almost all palpebral cancers to be excised and repaired under local anaesthesia. The new technique of full-thickness skin graft fixation with central and paracentral sutures instead of a tie-over bolus allows patients full activity immediately after the operation, thus making it possible for them to be operated upon as day cases. Over two-thirds of the patients in this series (79 out of 115) were successfully treated as day cases, thus countering the main criticisms of surgery, namely, the cost of hospitalisation and the possible unfitness of elderly patients to withstand prolonged general anaesthesia needed for complex surgical procedures. The surgical techniques advocated in this presentation are relatively simple procedures. In addition, surgery allows one to obtain histological confirmation not only of the diagnosis, but also of the adequacy of excision. Unlike radiotherapy, surgery does not produce serious and irreversible complications in the adjoining tissues which were originally uninvolved in the neoplastic process.

Lederman (1976) reports an overall rate of 13·6% of serious complications like lid necrosis, keratinisation of conjunctiva, corneal ulceration, radiation cataracts, and loss of eyes following radiotherapy. This is in addition to telangiectasia 12%; lid deformity 7%; epiphora 10%; and recurrence of about 10%. But Lederman's series was of a large sample of 896 patients of whom 90 patients were 'seen but not treated'. Rank (1973), in comparing the relative cost of surgery and radiotherapy for skin cancers, has shown that outpatient surgery under local anaesthesia is cheaper than radiotherapy.

The recurrence rate of 0·87% in this series compares well with results reported by other surgeons—Milverton (1977), 1·2%; Collin (1976), 2·3%; Holmström *et al.* (1975), 9%. Older *et al.* (1975) attribute their 100% cure rate to the frozen-section control they exercised in 72% of their cases. In the present series, with the recurrence rate of 0·87%, frozen section was utilised in 1 case only. It would appear that routine frozen-section control may need to remain an ideal unattainable for most surgeons in the United Kingdom at present owing to practical considerations.

Conclusion

This study shows that primary surgery can effectively deal with most palpebral cancers irrespective of the size and location of the tumour. Most of the surgical techniques described here are relatively simple one-stage procedures, capable of being performed under local anaesthesia on day-case basis, making surgery the initial treatment of choice for such tumours.

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A ptosis repair of aponeurotic defects by the posterior approach

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SUMMARY A simple posterior approach operation for correcting ptosis due to a disinsertion of the aponeurosis of the levator palpebrae superioris muscle is presented. Müller's muscle is restored to its normal length. Pull-out sutures are used which give some postoperative control of eyelid level and allow the procedure to be done under general anaesthesia if required.

Patients with an aponeurotic defect have a ptosis with good levator function, a thinned eyelid, and a high-arched lid fold. The affected eyelid remains lower than the other eyelid in all positions of gaze. Jones *et al.* (1975) first demonstrated the various aponeurotic defects which may occur in these patients (Figs. 1 and 2) and described their repair via an anterior skin approach under local anaesthesia. Although excellent results can be obtained by their technique, the results are not always predictable, and the eyelid level cannot easily be adjusted postoperatively. This paper describes a posterior approach operation for the repair of aponeurotic defects which can be done under local or general anaesthesia. Pull-out sutures are used, and the eyelid level can be adjusted postoperatively.

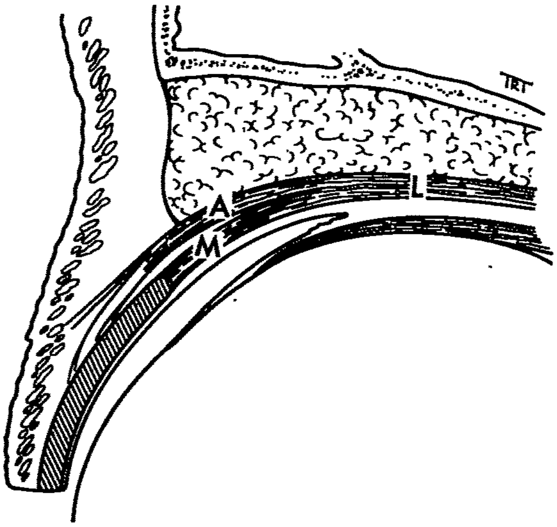

Fig. 1 *Normal upper eyelid anatomy.* L=*Levator palpebrae superioris muscle.* M=*Müller's muscle.* A=*Aponeurosis*

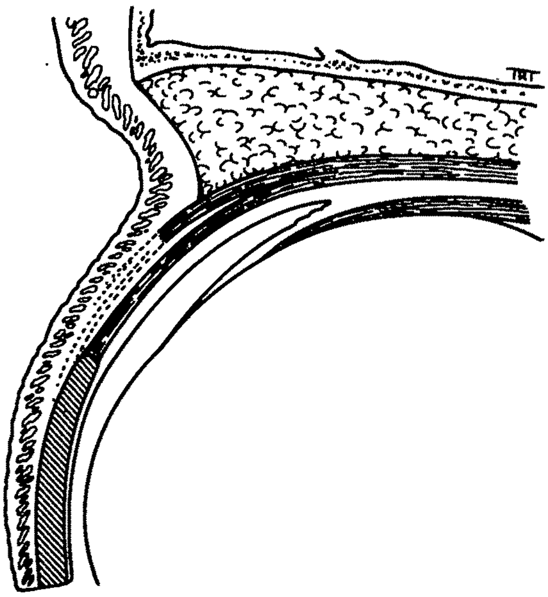

Fig. 2 *Diagram of disinsertion of the aponeurosis*

Procedure

The operation can be done under local or general anaesthesia. Local anaesthesia is preferred, as it is easier to identify the aponeurosis with the patient's co-operation. The eyelid is infiltrated subconjunc-

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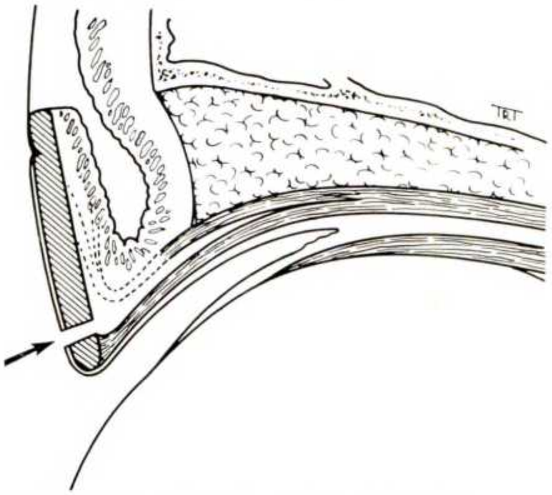

Fig. 3 *Incision through everted tarsal plate about 1–2 mm from its upper border*

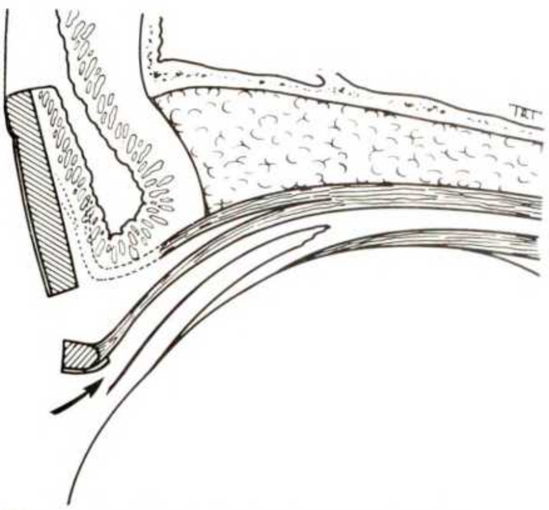

Fig. 4 *Separation of conjunctiva from Müller's muscle*

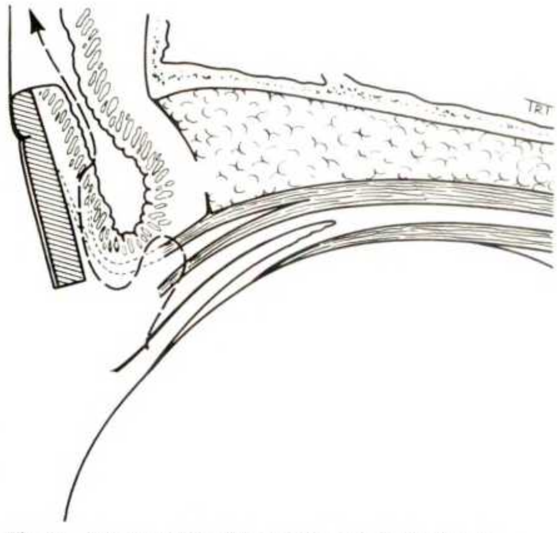

Fig. 5 *Position of double-armed posteriorly placed pull-out sutures*

tivally and subcutaneously with 2% lignocaine and 1/100 000 adrenaline. A 4 '0' black silk suture is placed in the tarsal plate and the eyelid everted over a Desmarres retractor. An incision is made through the tarsal plate about 1–2 mm from its upper border (Fig. 3). The conjunctiva is then separated from the lower part of Müller's muscle (Fig. 4). This plane is easily identified if the local anaesthetic has been injected here at the start of the operation. The conjunctiva is preserved, but the lower 2 mm of Müller's muscle with its tendon of insertion and the upper 1–2 mm of the tarsal plate are excised.

The aponeurosis is identified by its movement when the patient looks up and down if the operation is being done under local anaesthesia. Under general anaesthesia the orbital septum is identified first by its attachment to the orbital rim. The septum is then incised and the preaponeurotic fat pad is gently retracted. When the orbital septum has been divided, the superior surface of the aponeurosis can be examined to ensure that there is no defect posterior to the septal attachment. Both needles of 3 double-armed 5 '0' silk sutures are then passed through the conjunctiva about 2–3 mm from its cut edge, through the lower end of the shortened Müller's muscle, and through the lowest part of the aponeurosis which looks healthy. The sutures are then passed down the anterior surface of the tarsal plate and are brought out through the pretarsal orbicularis and skin at, or just below, the required position of the skin crease (Fig. 5). They are then tied over rubber or cotton-wool bolsters. This closes the conjunctiva, brings the lower cut end of Müller's muscle against the upper cut edge of the tarsal plate, and pulls healthy aponeurotic tissue into the pretarsal orbicularis muscle to reform the skin crease (Fig. 6).

The central suture is positioned first and tightened with a temporary knot. Under local anaesthesia this will give some idea of the elevation of the eyelid. If it is too low, the suture can be repositioned to pick up the aponeurosis more proximally. If the eyelid level is too high the aponeurosis may be picked up more distally or the suture tied less tightly if there is no distal aponeurotic tissue which appears healthy. The contour of the eyelid is then adjusted by the positioning of the medial and lateral sutures. No Frost suture is required, but an antibiotic ointment is liberally applied.

The time of suture removal is governed by the height of the eyelid postoperatively. The eyelid can be lowered by early suture removal and if need be the posterior wound can be opened with an iris repositor to let the eyelid down further. Usually the

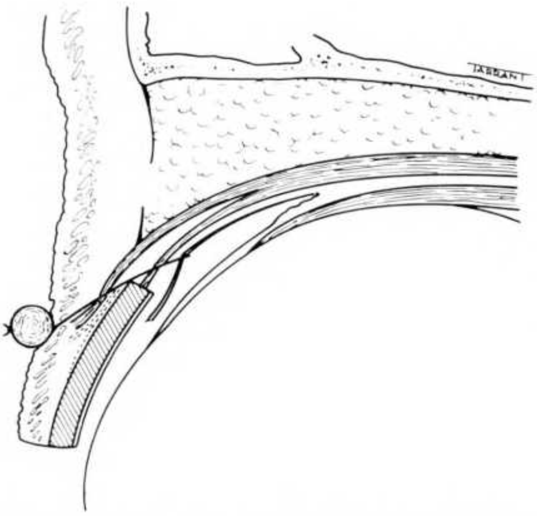

Fig. 6 *Eyelid structures reapposed after tying sutures over bolsters*

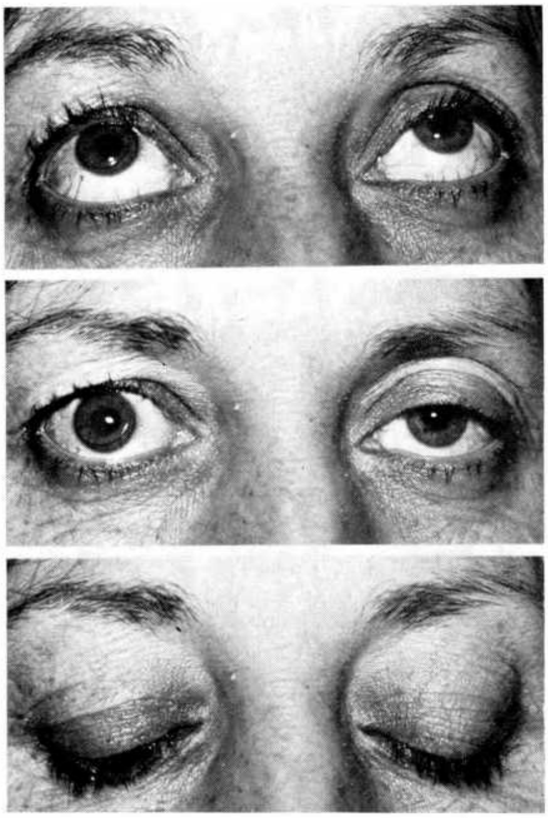

Fig. 7 *Preoperatively showing a left ptosis with the clinical feature of a disinsertion of the aponeurosis*

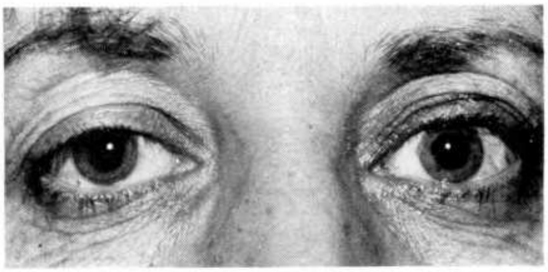

Fig. 8 *Nineteen days postoperatively showing over-correction of the left upper eyelid*

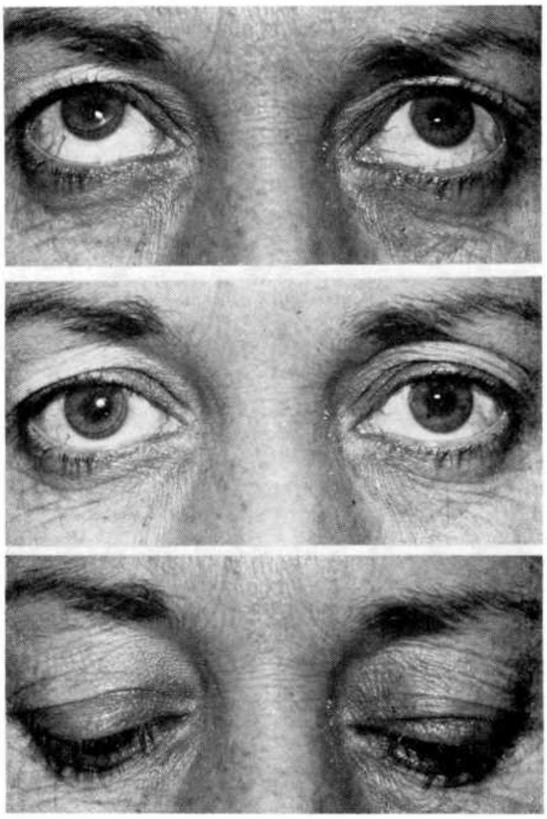

Fig. 9 *Four months postoperatively showing final results after massage*

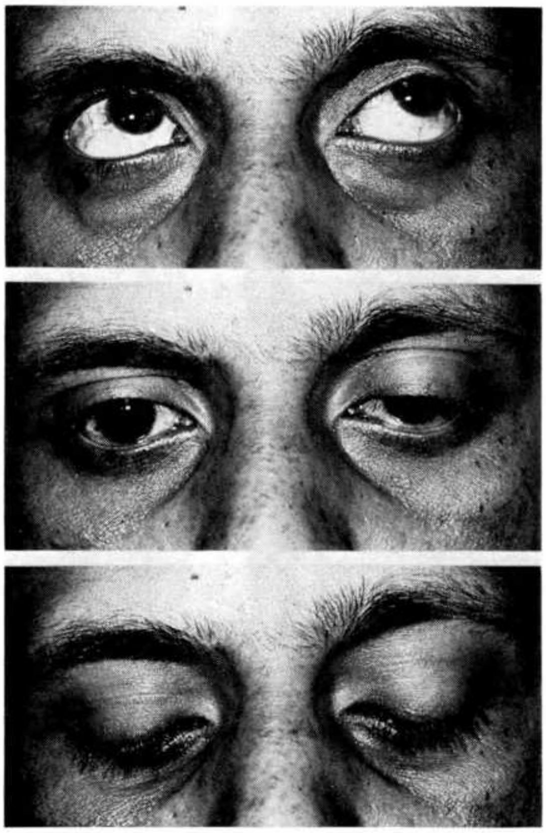

Fig. 10 *Preoperatively showing a left ptosis with the clinical feature of a disinsertion of the aponeurosis*

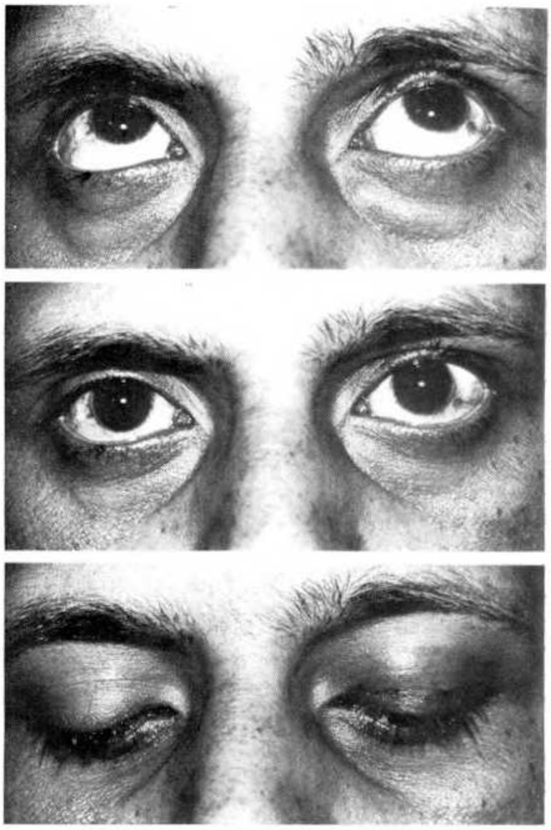

Fig. 11 *Four months postoperatively showing final result without massage*

eyelid is low postoperatively, and as the oedema settles the eyelid level rises. The sutures are left for 10 days unless the eyelid level is higher than the normal side before then. If this occurs, the sutures are removed at that time. After suture removal the eyelid level is closely watched. If it becomes too high (Figs. 7 and 8), massage will bring the eyelid level down and maintain it at the correct level (Fig. 9). If it is too low, the eyelid should be left severely alone until the postoperative fibrosis raises the eyelid to the required height (Figs. 10 and 11).

Results

Three patients have been operated on with this technique. All had 2–3 mm of an acquired ptosis with good levator function (10–14 mm), a high-arched lid fold, and a thin eyelid (Figs. 7 and 10). In the immediate postoperative period all the operated eyelids were low. The sutures were removed after 10 days, and the eyelid level continued to rise. In 2 cases, the eyelid reached and maintained the same level as the unoperated side (Fig. 11). In the other case the operated eyelid rose too high (Fig. 8), but the appropriate level was achieved and maintained by massage (Fig. 9). All have retained a satisfactory eyelid level, contour, and skin crease for 6 months postoperatively. Three more eyelids have since been operated on with initially good results, but the follow-up period is as yet too short for comment.

Discussion

The aim of this procedure is to correct the ptosis by reinserting the aponeurosis and to restore Müller's muscle to its normal length. The eyelid level will rise in patients with an aponeurotic defect if Müller's muscle is stimulated with cocaine (Jones *et al.*, 1975). This shows that Müller's muscle is not denervated. Histology and electron microscopy have not shown any defect of Müller's muscle cells (Kuwabara *et al.*, 1975) and there is no evidence of a disinsertion of the muscle (Collin *et al.*, 1978). Since the eyelid is ptotic, Müller's muscle must have stretched under the weight of the eyelid. It is logical to correct the effect of this stretching by shortening the muscle. If the aponeurotic defect is repaired by a standard anterior approach, Müller's muscle is not shortened as it is in the procedure reported here. Another benefit of this procedure is the use of pull-out sutures, which allow a measure of postoperative control of the eyelid level. This permits the operation to be done under general anaesthesia if required with a greater degree of accuracy than with the standard anterior approach.

The disadvantages of the posterior approach over the standard anterior approach are that an incision is made through the conjunctiva and some conjunctiva and tarsal plate are sacrificed even if the amount is minimal. A small loop of each pull-out suture does pass through the conjunctiva and could irritate the cornea, but this has not happened with any cases, probably because the sutures are above the upper border of the tarsal plate and are protected by the postoperative oedema of the conjunctiva. With the anterior approach it is easier to excise any excess skin and to examine the aponeurosis for any possible defect posterior to the orbital septum. Nonabsorbable sutures can be used with an anterior approach to suture the aponeurosis to the anterior tarsus, and this may reduce the chance of a recurrent disinsertion. The follow-up period with this series is too short to comment on the chance of recurrence after this operation.

This procedure is a modification of the ptosis operation described by Werb (1976). In his operation the ptosis is corrected by resecting a large part, or all, of Müller's muscle, and if this proves insufficient he then proceeds to the resection of part of the levator muscle. This is an excellent procedure for correcting many kinds of ptosis, but in patients with an aponeurotic defect it is not necessary to excise Müller's muscle. The operation described here restores the normal length of Müller's muscle and corrects the ptosis by reinserting the aponeurosis. This re-establishes the normal eyelid anatomy as much as possible (Collin *et al.*, 1978).

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British Journal of Ophthalmology, 1979, **63**, 591

Book reviews

A Short English-Swahili Medical Dictionary. By T. HEDLEY WHITE. Expanded and edited by C. E. Sorsbie, Nathan Mbwele, and Anne Ndubbi. Pp. 128. £3·50. Churchill Livingstone: London. 1979.

Swahili is a beautiful and growing language which is rapidly becoming the national tongue of Kenya. The purpose of this English/Swahili medical dictionary (in 2 volumes) is to translate standard medical vocabularies used all over the world by English-speaking peoples into Swahili and thus provide accurate communication between doctor, patient, and nurse. It is a pioneer piece of work because many of the technical medical terms have no absolute equivalent in the Swahili language, and Lady Sorsbie and her two collaborators Nathan Mbwele and Anne Ndubbi are to be congratulated on the time and care which they have spent with the author on this dictionary with a view to making it easier for the primary-case doctor to make a scientific diagnosis and apply appropriate treatment. Ophthalmology, which is said to have a sublanguage of its own, is well represented, as well it should be considering the amount of ocular disease which still exists in East Africa. Designed to fit into the pocket of a doctor's or nurse's white coat, the dictionary will prove a tireless medical auxiliary. We wish it every success.

S. J. H. MILLER

Ocular Toxoplasmosis and Pars Planitis. By T. F. SCHLAEGEL, JR. Pp. 378. $34·75. Grune and Stratton: New York. 1978.

This book of 378 pages tells the story of toxoplasmosis and pars planitis in some detail. It traces the advances in our knowledge contributed by many research workers.

Systemic toxoplasmosis is a protozoan infection of man and most of the animal kingdom. It is present worldwide, being more common in warm, moist, seaboard climates. It is usually asymptomatic, but when it is symptomatic it produces lymphadenopathy in man.

In 1923 Jankû, of Prague, described a boy who became blind at the age of 3 months and died of hydrocephalus. This infant had a granulomatous inflammation of the eyes due to the protozoan *Toxoplasma gondii*. In 1948 Sabin and Feldman presented their dye test, and in the same year Frenkel introduced the toxoplasmin skin test and showed its value in providing evidence of toxoplasmosis as a presumed cause of posterior uveitis. In 1952 Helenor Wilder demonstrated *T. gondii* in tissue sections in 53 adults who showed retinochoroiditis, and 30 of these cases had previously been diagnosed as probable tuberculosis.

The feline is the definitive host of toxoplasma but the organism is ubiquitous. The discovery of the coccidial stage of toxoplasma in intestines of cats and of oocysts excreted in cat faeces suggests that the oocyst form of the parasite may be the major source of transmission. Since there is an increasing prevalence of positive serological titres with increasing age it would appear that many people acquire the disease at some time during their lives.

In congenital systemic toxoplasmosis the organism is transmitted to the fetus from the maternal circulation or a focus in the uterus. It has a predilection for nervous tissue. Characteristic features are an encephalomyelitis succeeded by areas of calcification in the brain and bilateral chorioretinal lesions often affecting the maculae. High antibody titres are found in sera from mothers who have just been delivered of diseased children, but the mother does not give birth to more than 1 child with congenital toxoplasmosis. Once a woman has had toxoplasmosis and has become immune she cannot give it to any subsequent children. Most authorities now think that ocular toxoplasmosis is usually congenital in origin, and as 3000 of the 3 million babies born in the United States each year have congenital toxoplasmosis there is still a sizeable medical problem to be solved.

Wilder pointed out that it is not the level of serum titre that is important in the diagnosis of ocular toxoplasmosis but rather the presence of a positive skin test or dye test. A rising titre in ocular toxoplasmosis does not occur except in those rare patients with acquired systemic toxoplasmosis complicated by toxoplasmic retinochoroiditis. The vast majority of cases of toxoplasmic retinochoroiditis are of congenital origin. Toxoplasma organisms lie dormant as cysts in the retina, to be awakened later. The incidence of ocular toxoplasmosis in posterior uveitis is variously estimated from 25% (Perkins) up to 70% (Cassady).

Satellite foci are most helpful in pointing to the presumed aetiology of the toxoplasmosis, since most cases of toxoplasmic retinochoroiditis occur at the edge of a previous scar. It affects patients between the ages of 11 and 40 years and is often unilateral and single. Cells appear in the vitreous and disappear with recovery. The diagnosis should be based on a typical clinical picture plus laboratory evidence of toxoplasmosis. The mainstay of the diagnostic armamentarian is still the Sabin-Feldman dye test.

In treatment at least one antimicrobial agent must be used if corticosteroids are employed because of the hazard of generalised toxoplasmosis in the immunologically compromised patient. The common routine is to give triple sulphonamides in a dosage of 3 500-mg tablets every 6 hours with 100 mg of pyrimethamine twice the first day and 25 mg twice a day thereafter. It is important that the patient receives 3 mg of citrovorum factor or folinic acid once weekly.

Pars planitis was first described by Schepens in 1950 after the introduction of the binocular ophthalmoscope. The condition involves retinal phlebitis with leakage into the vitreous and the late development of collagen in the vitreous. It accounts for 4 to 8% of patients with uveitis, and it affects mainly children and young adults.

A child with uveitis has about 1 chance in 5 of having pars planitis. There is no sex predeliction. Two-thirds of the cases are bilateral. Symptoms and external signs are minimal. The type of complaint consists of seeing black spots, strands, or thin veils or having blurred vision. Most cases in the population at large, perhaps as many as 80%, do not need any treatment. In cases lasting from

15 to 26 years severity is no greater than in the less chronic.

If vision is found to be reduced at first examination it is usually due to posterior subcapsular cataract, organised anterior vitreous opacities, macular cystic changes, or disc oedema or a combination. If keratic precipitates are kept to a minimum and the patient is comfortable, flare and cells in the anterior chamber with a moderate number of cells in the vitreous should be discounted.

One of the most typical features of a pars planitis is leakage of fluorescein into the vitreous apparently from the retinal veins and from neovascularisation in the ciliary body region. The vitreous is quickly filled with fluorescein. It is only later that dye is seen in the anterior and posterior chambers. This rapid leakage of fluorescein dye into the vitreous adjacent to the ciliary body is most characteristic of the disease. It is always difficult to define an end point, because cells in the vitreous may persist for many years and relapses can occur.

Therapy on the whole is disappointing, though corticosteroids have a place in the treatment of most cases. Immunosuppressents should be employed only in severe cases in which corticosteroids have failed to have any effect. Diathermy, cryocoagulation, and photocoagulation have nothing to offer. S. J. H. MILLER

Directory of Agencies Serving the Visually Handicapped in the US. 30th edn. Pp. 436. $10·00. American Foundation for the Blind: New York. 1978.

This the 20th edition provides over 400 pages of condensed information. The *Directory* makes no attempt to evaluate or endorse any of the organisations or services that are listed, nor does it claim to be absolutely comprehensive, for it lists only nonprofit organisations. Clear instructions on how to obtain further information are given in the introduction.

There are two sections, the first listing services State by State. These are classified into educational services, library services, and rehabilitation services. Comprehensive information is given on criteria for eligibility, how the agency is funded—that is, State, charity, or client fees—and precisely what services are available. The potential client who needs, for example, braille or mobility training is able to make an independent informed decision and can approach the named director personally. No attempt is made to quantify or evaluate specific services.

Section 2, entitled 'Supplementary Lists of Specialized Agencies and Organizations', seems to be aimed at professionals of various disciplines working with the visually handicapped. State by State it lists research organisations, guide dog schools, and professional preparation centres. The largest subsection is devoted to low-vision services, with hospital clinics and university departments (both ophthalmology and optometry) and fee-based private facilities being included. Again the discriminating reader should be able to use the information provided to decide which of the accessible facilities is the most appropriate.

Few criticisms of this useful volume can be made. It should perhaps be available in large print or braille, and obviously any such directory is inevitably out of date before the print is set. But so much information so readily accessible would be extremely useful in any eye clinic and social worker's office. It is to be hoped that a similar directory will be made available for the United Kingdom. JANET SILVER

Ocular Pharmacology. 4th edn. WILLIAM H. HAVENER. Pp. 762. £37·80. Henry Kimpton: London. 1978.

The 4th edition of this popular textbook follows the pattern of previous editions. The first part covers drugs in ophthalmic practice and the second part deals with current ophthalmic therapy. There is a useful chapter on evaluation of the therapeutic response, including placebo and reassurance therapy. This is followed by a chapter on routes of administration which includes soft lens and membrane delivery.

The drugs are described in alphabetical order of therapeutic groups. In general the pharmacological action is described from a clinical approach, experimental evidence being kept to the minimum essential for this purpose. There is a good description of the clinical use of each drug, so that the title could have been 'Ocular Pharmacology and Therapeutics'.

Generous references are supplied throughout (2573 references) and the illustrations are well chosen, often from the original reference. Toxic reactions are well described. As with any such book taking time to revise and print, there are bound to be omissions, the obvious example being that there is no mention of the beta blocker timolol.

The author admits to a number of healthy prejudices, such as preferring local to general anaesthesia for many forms of surgery, being unconvinced of the beneficial value of photocoagulation in diabetic retinopathy, and preferring fascia to silicone implants in retinal detachments. The chapter on general anaesthesia includes a section on cardiac arrest. In addition to the larger groups of drugs there are useful chapters on the smaller groups such as adhesives, biological drugs and alpha-chymotrypsin.

The second part, on current therapy, includes chapters on cataract, external diseases, glaucoma, and infection. There is a fascinating description of all the different drugs, some with opposite action, used to treat traumatic hyphaema. The conclusion would appear to be that the spontaneous course of hyphaema is unchanged by any form of medical management, including bed rest.

This whole book makes most enjoyable reading, which is not usual in pharmacology textbooks, and can be thoroughly recommended. S. J. CREWS

Contact Lenses. A Clinical Approach to Fitting. By ROBERT H. HALES. Pp. 248. $26·50. Williams and Wilkins: Baltimore, Maryland. 1978.

Up to date and practical, this book deals with the fitting of all available contact lenses in a clear step-by-step manner. There are useful chapters on contact lens solutions and the choice of contact lenses. The chapter on fitting hard contact lenses includes the Dyer and Boyd methods. Spun-cast and lathe-cut soft lenses are discussed with the fitting methods of both, and also the use of therapeutic soft lenses. There are chapters on CAB and silicone lenses, scleral lenses, and intraocular lenses. This is a comprehensive book, recommended for anyone interested in fitting contact lenses.

M. S. WILSON

Handbook of Pediatric Ophthalmology. Ed. STEPHEN S. FEMAN and ROBERT D. REINECKE. Pp. 196. £12·65. Grune & Stratton: New York. 1978.

This handbook is intended to supply the reader with a broad overview and a basic understanding of paediatric ophthalmology. The writing of it was stimulated by the editors' contact with medical students at the stage of grasping the basic problems in ophthalmology. The book succeeds in its intention and will be a useful introduction for medical students and also to others such as orthoptists, opticians, paediatricians, and other readers interested in children with eye disease. There is a useful chapter on principles and examples in ophthalmic genetics, which again will be of interest to those trying to grasp the subject. The references are basic and useful, but the illustrations, mainly drawings, may to some degree detract from the book. However, the book is well balanced and should prove popular. DAVID TAYLOR

Therapeutic Systems: Pattern-Specific Drug Delivery: Concept and Development. By KLAUS HEILMANN. Pp. 143. DM38. George Thieme Verlag: Stuttgart. 1978.

This short book is a revised English-language edition of a text originally published in German in 1977. It outlines the principles behind, and applications of, metered and 'organ-specific' drug delivery systems. As a large section describes the application of this principle (used clinically as the Ocusert system) to the eye, the book is of considerable interest to ophthalmologists. The author is professor of ophthalmology in Munich and secretary general of the International Society for the Advancement of Therapeutics. Many of the principles and devices he outlines were developed by the ALZA Corporation, founded by Al Zaffaroni, whose leading role in this field the author acknowledges.

The book may be divided into 3 sections. The first includes definitions, giving explanation of words such as 'biopharmaceutics' and 'liberation', and differentiating between pharmakokinetics and pharmakodynamics. It describes the principle behind various types of 'therapeutic systems' and devices, by which metered-dose continuous delivery of a drug may be delivered either locally or systemically. The second section describes therapeutic systems for systemic use such as the infusion system for intravascular infusion of drugs in solution, the gastrointestinal therapeutic system (a trial of the acetazolamide gastrointestinal therapeutic system being recently reported), and the transdermal therapeutic system. The third section describes therapeutic systems for local use. Ophthalmic therapeutic systems are described in some detail. When describing the (pilocarpine) Ocusert, the author draws on his own experiences. The possible role of ocular therapeutic systems in the treatment of infective and inflammatory disease of the eye is also described.

The book concludes with a glossary of biopharmaceutical terms and a useful bibliography. It is easy to read and makes good use of diagrams to illustrate points made in the text. It should make interesting reading for the general ophthalmologist who wishes to improve his knowledge of the background and principles by which these 'therapeutic systems' work.

ROGER HITCHINGS

Obituary

J. A. Corkey, MD, FRCSI, DOMS

Mr J. A. Corkey, formerly senior ophthalmic surgeon at the Eye Clinic, Royal Victoria Hospital, Belfast, died suddenly on 7 March. He was 72.

Joseph Allison Corkey was born in the Manse, Cullybackey, Co. Antrim. Educated at Royal Belfast Academical Institution and Queen's University, Belfast, he graduated in medicine with first class honours in 1930. He represented his school and university at rugby. After holding house appointments at the Royal Victoria Hospital he was appointed a demonstrator in pathology for a year, during which time his interests turned to ophthalmology. After postgraduate study and training in Vienna and the Western Ophthalmic Hospital, London, he obtained the MD, FRCSI, and DOMS.

Mr Corkey was appointed to the ophthalmic staff of the Benn Ulster Eye and Ear Hospital in 1934 and ophthalmic surgeon to the Royal Victoria Hospital in 1939. He was senior ophthalmic surgeon at the Eye and Ear Clinic, Royal Victoria Hospital, from its opening in 1965 until his retirement in 1972. During this period he was also lecturer in ophthalmology to Queen's University, Belfast, and was responsible for undergraduate and postgraduate training, making notable contributions to the specialty. A member of many medical societies, he was also an elder of the church, at which his father had formerly been senior minister, and an enthusiastic Rotarian. As a member of many committees his quiet and considered opinion was always welcome. He was honorary secretary for many years of the Board of Governors of 'Inst', and a member of convocation of Queen's University, Belfast. Active in BMA matters, he was formerly chairman of the Belfast Division and chairman of the Northern Ireland Council. In recognition of his services he was elected a fellow of the Association in 1971. He was also chairman of the Medical Staff Committee of Royal Victoria Hospital during 1963–65, and was a past president of the Ulster Medical Society.

In addition to his active involvement in many medical and social activities he retained a life-long interest in his specialty and was the Northern Ireland representative on the Faculty of Ophthalmologists for many years and the Ophthalmic Group Committee of the BMA. He was also interested in the more recently formed Irish Faculty of Ophthalmology and was an early member. As a council member of the Irish Ophthalmological Society he was a regular attender and contributor at the annual general meetings. There was universal appreciation of his friendly and impressive manner when as president of the IOS in 1976 he led the visiting party to the ophthalmic clinics in America and then on to a joint meeting with the New England Ophthalmological Society in Boston. He enjoyed his usual Saturday morning golf at Belvoir, and was never happier than when he was with his family and involved in their activities.

Allison Corkey will be sadly missed by his family, large circle of friends and many members of the large community that he served so well. He is survived by his wife, Kathleen, three daugnters, and a son, who is also a doctor. V.A.F.M.

Notes

Change in style of references

In accordance with the Vancouver agreement many medical journals are to standardise the instructions they issue to authors on the preparation of articles. References will be cited by the numerical system already familiar in many journals, including the *British Medical Journal.* A paper (or book) cited in the text is referred to there by a superscript number. In the list of references the papers (or books) appear in the numerical order in which they are first cited in the text, not in alphabetical order by authors' names. For convenience in preparing the typescript the reference number may be typed between parentheses on the line, not superscript. The titles of journals will be abbreviated in accordance with the style of *Index Medicus.* In the typescript they should either be abbreviated in that style or given in full. This journal will change to the numerical system from the first issue of 1980. *Authors submitting papers are asked to adopt it now in order to facilitate editing.* Three examples follow:

1 Green A B, Brown C D, Grey E F, A new method of measuring the blood glucose. *Br J Ophthalmol* 1980; 64: 27–32.

2 Green A B, Brown C D, *Textbook of Medicine.* London: Silver Books, 1980.

3 Grey E F, Diseases of the pancreas. In: Green A B, Brown C D, eds. *Textbook of Medicine.* London: Silver Books, 1980; 349–362.

Copies of the Vancouver agreement (50p, post free) are obtainable from the Publishing Manager, British Medical Journal, BMA House, Tavistock Square London WC1H 9JR.

European Glaucoma Society

The First Symposium of the European Glaucoma Society will be held on 18–20 April 1980 in Brighton. It will take place in the William IV room of the Brighton Pavilion and accommodation has been arranged at the Old Ship Hotel nearby. For details, conference registration, and hotel booking documents apply to Mr Redmond Smith, 2 Harley Street, London W1. Documents will be sent out in June and July. The number of delegates is limited to 200, so early booking is essential.

New York Seminar

The Department of Ophthalmology at Park Ridge Hospital, Rochester, New York, will hold the fourth annual Ophthalmic Seminar on 10–11 August 1979. Topics will be Current Concepts in Vitrectomy, Paediatric Ophthalmology, and Diseases of the Anterior Segment. Further information from Ms. Katherine Sgabelloni, RN, Coordinator, Ophthalmic Services, Park Ridge Hospital, 1555 Long Pond Road, Rochester, New York 14626, USA.

Retinal and vitreous disorders

An international symposium on the practical management of retinal and vitreous disorders will be held at Gleneagles Hotel, Perthshire, Scotland, on 4–8 May 1980. Details from Mrs Allene Gearce, Department of Ophthalmology, Ninewells Hospital and Medical School, Dundee DD2 1UB, Scotland.

Metabolic eye disease

The Fourth Symposium of the International Society on Metabolic Eye Disease will be held in Cairo, Egypt, on 11–13 February 1980 under the auspices of President Muhammad Anwar El-Sadat. The programme will include discussion of nutritional metabolic eye disease, metabolic cataracts, and the role of metabolism in ocular infectious diseases. A second session of the symposium will be held in Jerusalem, Israel, on 18–21 February 1980 to discuss diabetic retinopathy, mucopolysaccharidoses, and metabolic retinal and corneal disorders. For inquiries and submission of free papers contact Programme Chairman, Heskel M. Haddad, MD, 1200 Fifth Avenue, New York, New York 10029, USA. For travel information contact Garber Travel, 1406 Beacon Street, Brookline, Massachusetts 02146, USA.

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This Symposium, like the three previous Mackenzie Symposia which were published in book form, is edited by Mr J. Stanley Cant of the Tennent Institute of Ophthalmology, Glasgow. This Part also contains the Proceedings of the Scottish, Irish, and regional ophthalmological societies, the full text of the Symposium on Retinal Therapy held at St. Thomas's Hospital, London, in November 1977, and the Annual Index for the year 1977.

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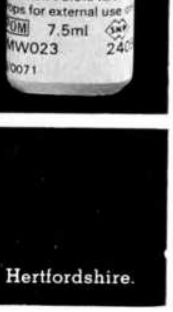

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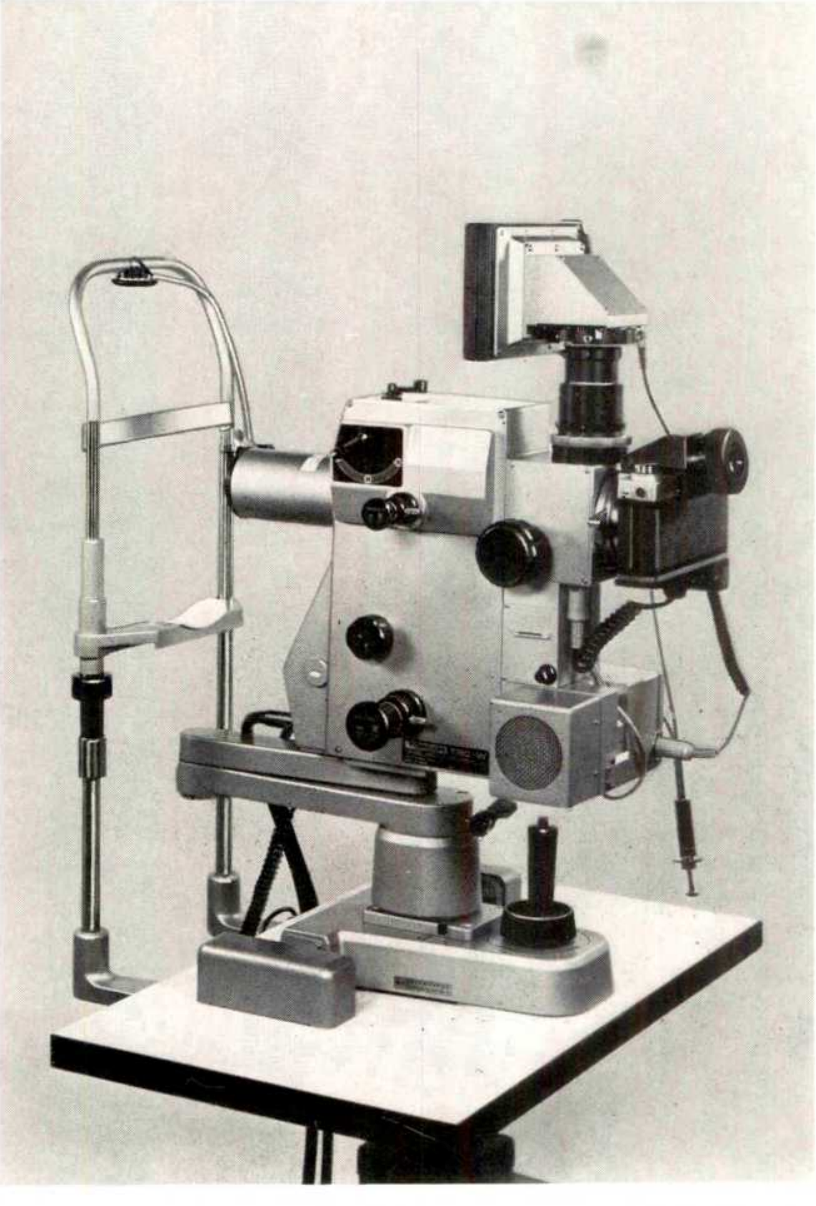

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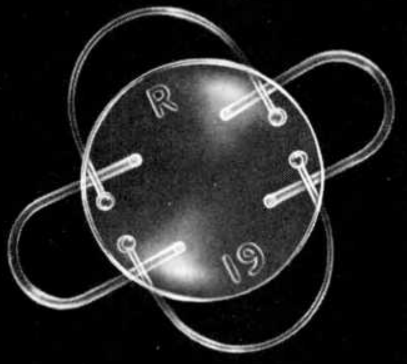

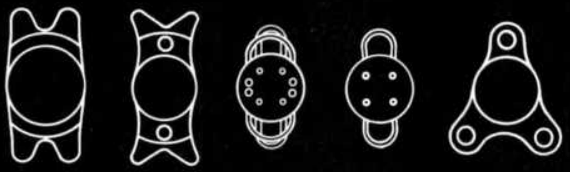

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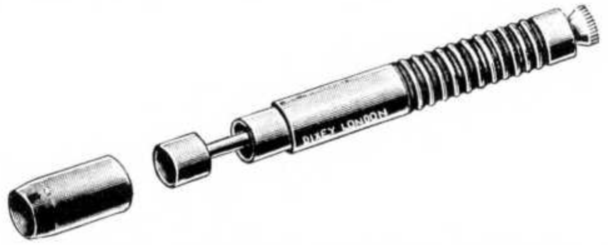

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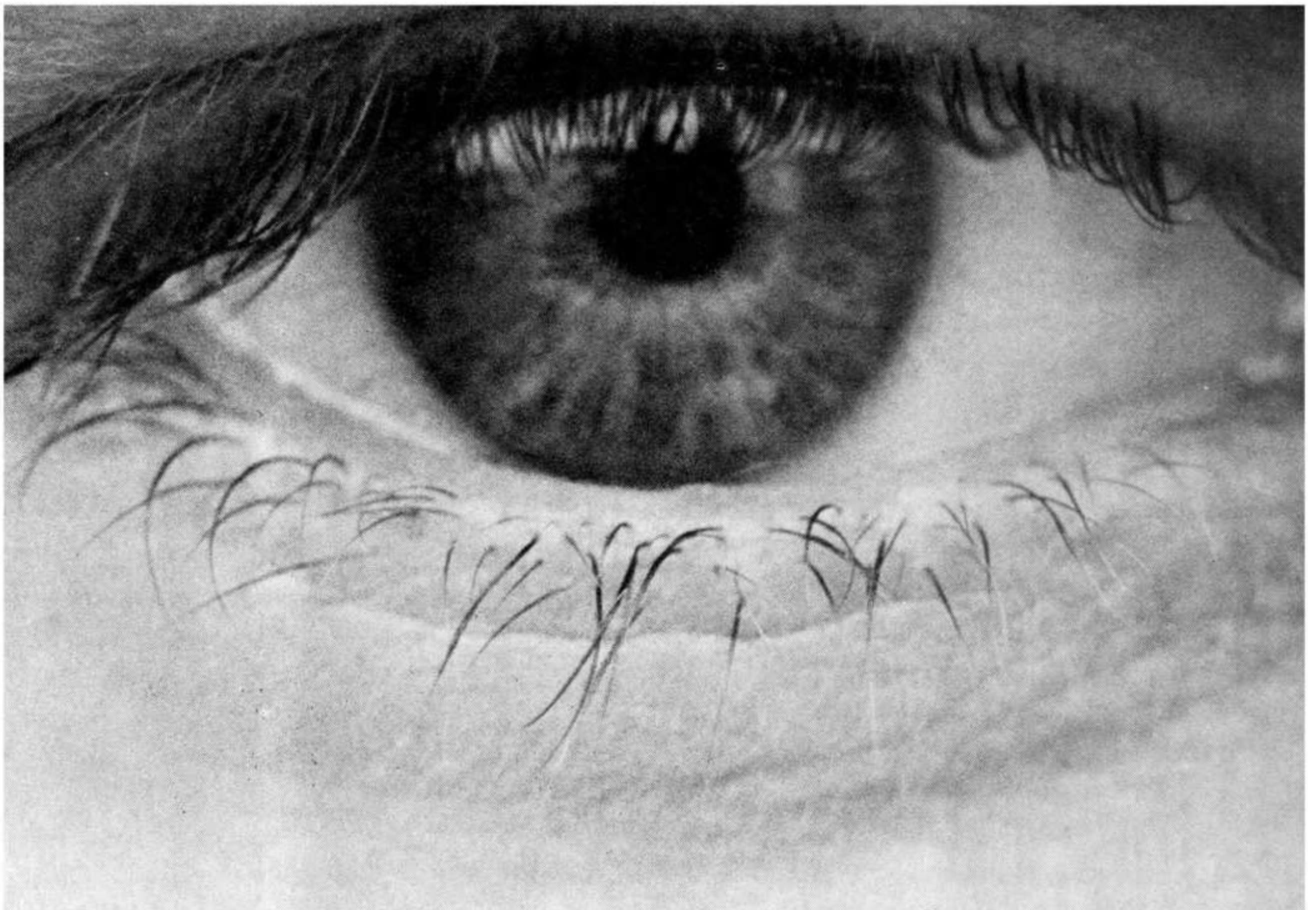

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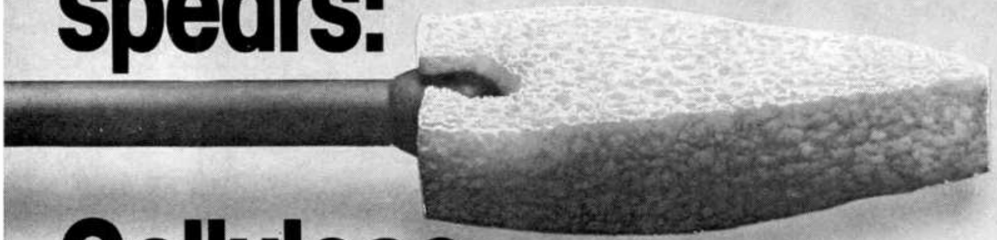

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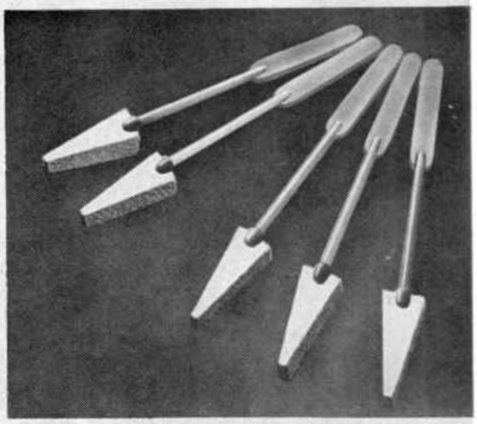

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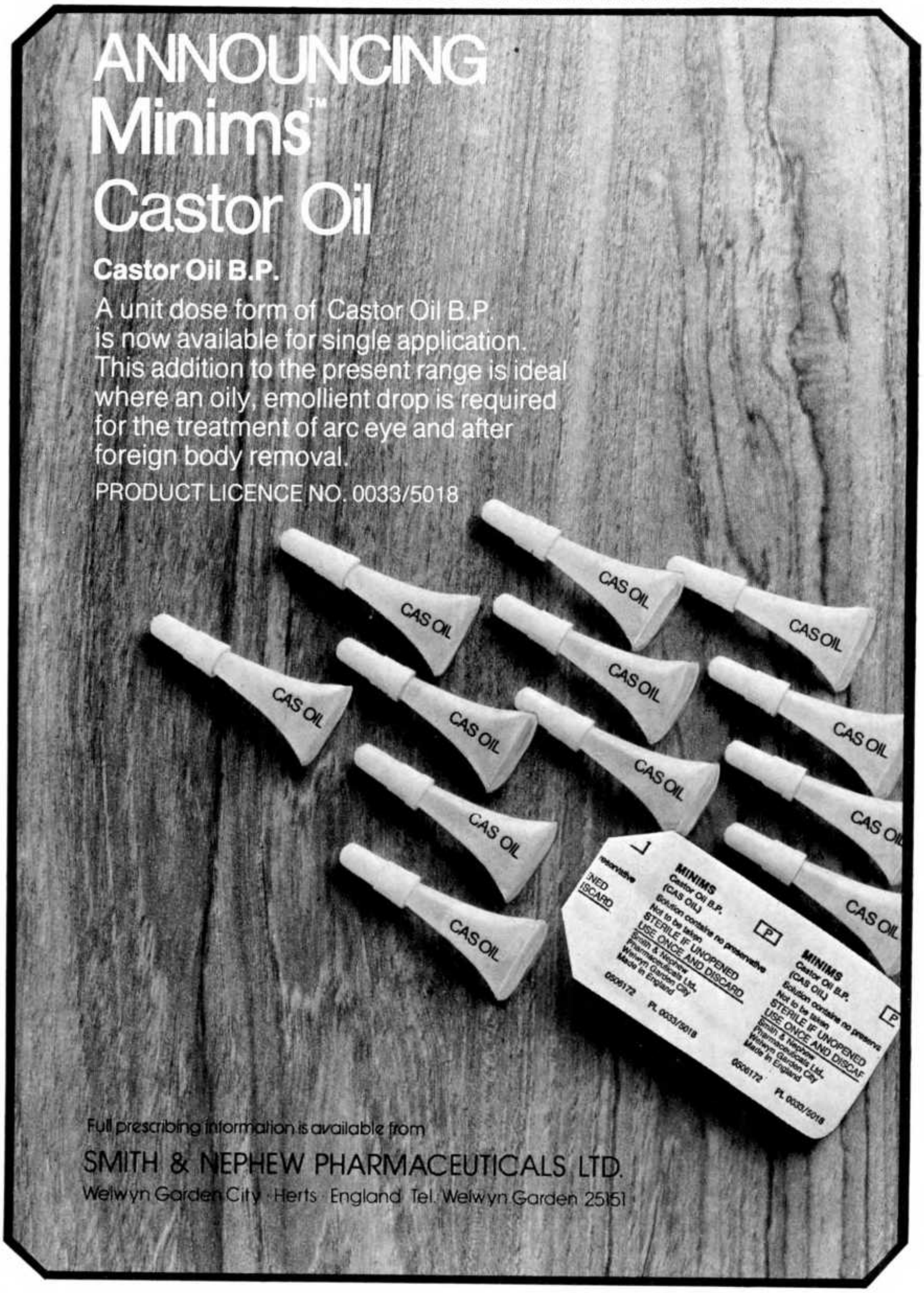

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British Journal of Ophthalmology, 1979, **63**, 595

Editorial: Primary optic nerve meningioma

Meningiomas arising from the meningothelial cells surrounding the intraorbital portion of the optic nerve are uncommon. They usually present with loss of vision, optic disc oedema, progressive optic atrophy, and in many cases opticociliary shunt vessels. In the early stages proptosis is often minimal or absent, though it may become apparent later in the disease process. Several series of cases have been reported (Craig and Gogela, 1949; Henderson, 1973 Wright, 1976). They have shown that these tumours occur predominantly in middle-aged women and are rarely encountered in children.

The conflicting report of Karp *et al.* (1974) of 25 cases of primary optic nerve meningioma stated that 40% of their cases occurred in children and young adults below the age of 20 years. A possible cause for this discrepancy is put forward by Cooling and Wright in this issue of the *BJO* (p. 596). They consider that the arachnoid hyperplasia seen in association with glioma can readily be mistaken for a primary optic nerve meningioma. In the case reported a piece of normal nerve remote from a glioma was excised and reported by the histopathologist as a primary optic nerve meningioma based on arachnoid proliferation which included the presence of psammoma bodies. Subsequently the remainder of the optic nerve with similar tissue surrounding a glioma was removed.

The diagnosis of optic nerve meningioma in children can be extremely difficult and should be made with great care. It is particularly dangerous to base this diagnosis on histopathological grounds alone or when the clinical details are rudimentary and the clinical investigative techniques poor or absent. As in so many clinical fields, there is an increasing need for co-operation between the ophthalmologist, who has access to extremely sophisticated methods of investigation, and the histopathologist. There is a need for the latter to play an increasing part in the diagnosis and clinical management of a whole range of puzzling clinical entities.

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British Journal of Ophthalmology, 1979, 63, 596–599

Arachnoid hyperplasia in optic nerve glioma: confusion with orbital meningioma

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SUMMARY A case is reported of an optic nerve glioma with a marked degree of arachnoid hyperplasia which was initially diagnosed as an optic nerve meningioma. Hyperplasia of the arachnoid was also the underlying cause for expansion of the optic canal. The relationship between arachnoid hyperplasia in optic nerve glioma and meningioma of the optic nerve sheath in childhood is discussed.

Arachnoid hyperplasia is a meningeal response which is often seen in association with gliomas of the anterior visual pathways. This case report concerns an example of exuberant arachnoid hyperplasia affecting the intracranial and intracanalicular portions of the optic nerve excised through a transcranial approach. The specimen comprised a normal optic nerve surrounded by meningothelial cells and psammoma bodies and was interpreted as a primary optic nerve meningioma. An optic nerve glioma was subsequently removed through a lateral orbital approach, so that the true diagnosis was established. This paper discusses the implications of these findings and offers an explanation for the high incidence of primary optic nerve meningiomas in children reported by Karp *et al.* (1974), figures at variance with those previously published from this hospital.

Case report

An 8-year-old girl first presented in April 1974 to Moorfields Eye Hospital. There was a 4-month history of left sided painless proptosis and a left convergent squint. She had previously been healthy. The visual acuity in the left eye was reduced to 6/36 with a left convergent squint of 40°. There were 3 mm of axial nonpulsatile proptosis, upward movement of the eye was restricted, and there was a marked left afferent pupillary defect. The left optic disc appeared hypoplastic, with swelling of the nerve head visible in the upper nasal quadrant. The right visual acuity was 6/6, with intact central and peripheral visual fields. There were no other abnormal neurological findings and specifically no stigmata of neurofibromatosis.

Plain radiographs of the optic foramina showed enlargement of the left canal with a regular and intact margin. The right optic foramen was normal. Widening of the left optic canal throughout its length was confirmed on axial polytomography. B-scan ultrasonography showed an acoustically homogeneous mass arising from the left optic nerve. The pattern visual evoked response showed a normal response on the right side but diminished amplitude and increased latency on the left.

An exploratory biopsy of the left optic nerve was undertaken in April 1974, revealing a bluish distension of the optic nerve sheath. Histopathological examination showed an area of meningothelial cells, fibrous tissue, and a few well-differentiated glial cells. There was no evidence of optic nerve glioma in the sections examined.

In October 1977 the visual acuity in the left eye was further reduced to 6/60. Proptosis of the left eye had increased to 10 mm with 8 mm of inferior displacement. The left optic disc showed generalised pallor, with diffuse nerve fibre loss in the retina visible on red-free ophthalmoscopic examination. Computerised axial tomography showed an ill-defined expansion of the left optic nerve (Fig. 1). The density of the lesion was considerably enhanced after the administration of contrast medium (Conray 420). The intracranial scan with particular reference to the parasellar region was normal. An air encephalogram showed a normal intracranial optic nerve on the left side.

A left frontal craniotomy was performed in November 1977. The chiasm and intracranial optic nerves appeared entirely normal. Emerging from the left optic canal was a greyish mass which encircled

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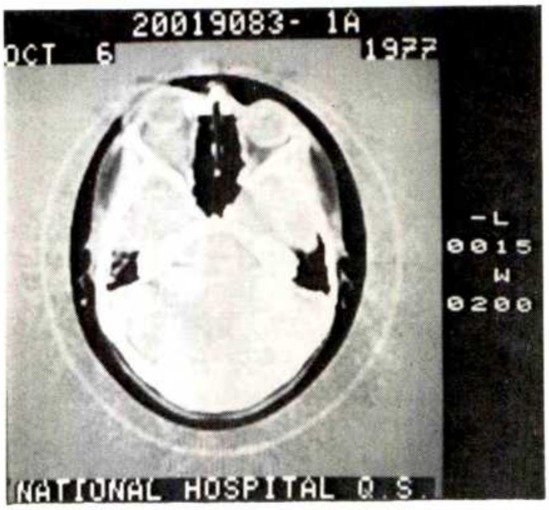

Fig. 1 *Computerised tomographic scan shows large irregular mass in left retrobulbar space*

the optic nerve. Transection of the left optic nerve was performed at its junction with the chiasm and reflected forwards through a deroofed optic canal. The nerve was divided 1 mm anterior to the common tendon within the orbit.

Histopathological examination showed a normal optic nerve with an extensive collar of meningothelial cells and an intermingling of psammoma bodies. No evidence of glial hyperplasia or astrocytic glioma was seen throughout the intracanalicular or intracranial portions of the optic nerve. The diagnosis was a primary optic nerve meningioma.

In February 1978 a left orbitotomy was carried out via a lateral canthotomy. A large bluish globular mass continuous with the optic nerve was excised, and the optic nerve was divided flush with the globe. Fig. 2 shows the eccentric disposition of the tumour in relation to the optic nerve. Histological examination showed a typical grade I (Reese, 1976) astrocytic glioma of the optic nerve with extensive meningothelial cell proliferation in a whorled pattern and numerous psammoma bodies.

The patient was last examined 12 months after orbitotomy. There was no evidence of orbital recurrence or intracranial tumour, and the cosmetic appearance was good.

Discussion

Proliferation of arachnoid cells was observed by Verhoeff (1922) in several cases of optic nerve glioma. Distension of the perineural space by meningothelial cells was seen proximal and distal to the underlying glioma. Proliferation of contiguous tissue elements has been noted in the connective tissue trabeculae of the optic nerve (Kiel, 1923), in the capillaries within the optic nerve glioma, and the supporting tissues of the arachnoid. Davis (1940) emphasised the development of arachnoid hyperplasia, which appeared to follow extension of the glioma beyond the pial sheath of the optic nerve. Arachnoid hyperplasia is seen as an orderly arrangement of meningothelial or cap cells with or without psammoma bodies. Extension of the glioma or of the arachnoid hyperplasia rarely occurs beyond the dura mater.

Examples of prolific meningeal hyperplasia have formed the basis of several case reports. Walter and McKenney (1964) reported arachnoid hyperplasia with cyst formation as the cause for progressive proptosis following excision of an optic nerve glioma. Sanders *et al.* (1965) described a case of extensive arachnoid hyperplasia within the orbit in an intracranial optic nerve glioma in which invasion of the orbit by glioma was not demonstrable.

The possibility of diagnostic confusion between arachnoid hyperplasia accompanying a glioma, and orbital meningioma has previously been raised (Hogan and Zimmerman, 1962; Walsh and Hoyt, 1969). The case reported here illustrates the manner in which meningioma may be diagnosed when hyperplastic arachnoid remote from the glioma is examined. The histological appearance complete with the presence of psammoma bodies and the normal underlying optic nerve made the histological diagnosis inevitable, while the assessment was made

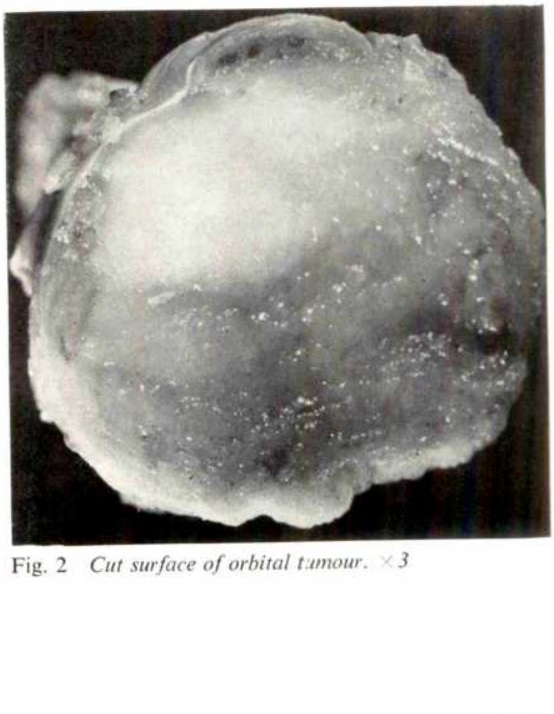

Fig. 2 *Cut surface of orbital tumour.* ×3

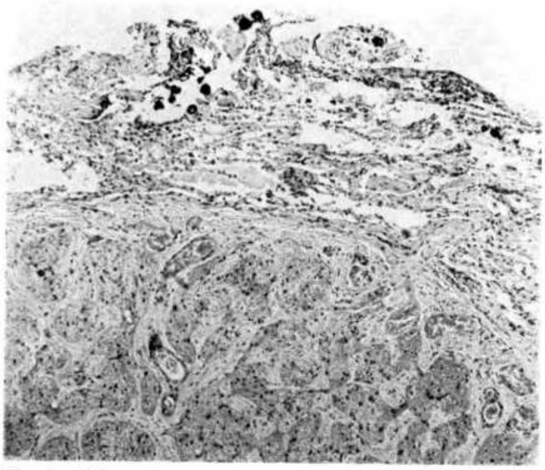

Fig. 3 *Photomicrograph of transverse section of intracranial portion of optic nerve. There is meningeal hyperplasia in which psammoma bodies are seen. Haematoxylin and eosin, × 44*

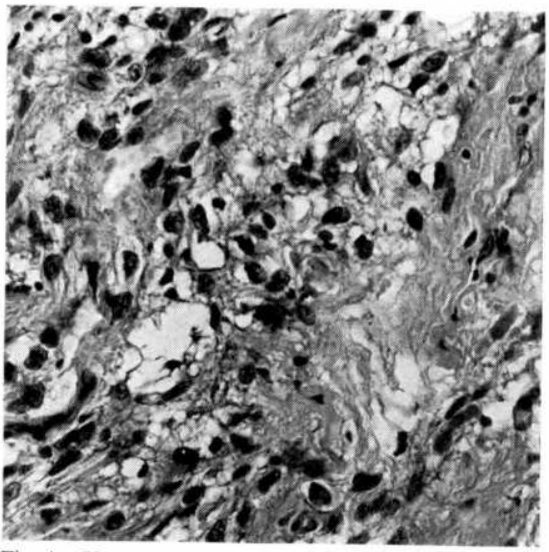

Fig. 4 *Photomicrograph of glioma showing neoplastic proliferation of glial cells together with a fibrillary component. Haematoxylin and eosin, × 270*

without the full clinical history and findings. This case also demonstrates that expansion of the optic canal can be caused by arachnoid hyperplasia rather than extension of the glioma beyond the confines of the orbit. Spencer (1972) recorded a similar cause for optic canal enlargement in an orbital glioma.

The origin of orbital meningiomas from the arachnoid sheath of the optic nerve was at one time questioned (Verhoeff, 1932). Several series of orbital meningiomas have now been reported which establish the optic nerve sheath as the commonest origin of primary intraorbital meningiomas. Craig and Gogela (1949) reported 9 meningiomas arising from the optic nerve sheath. Henderson (1973) considered 11 of 14 primary tumours to have arisen from the optic nerve sheath within the orbit in patients seen at the Mayo Clinic over an 18-year period. Reese (1976) has stated that primary orbital meningiomas account for one-third of all primary tumours of the optic nerve. In the series of primary optic nerve meningiomas previously reported from this centre (Wright, 1976) a total of 15 cases of primary optic nerve meningioma was reported. It was emphasised that meningiomas arising from the optic nerve within the orbit were seen in adults with a female preponderance. Since that report a further 5 cases have been treated. Only 1 child aged 11 years has been encountered out of the 20 patients examined. This is in agreement with several previously reported series (Craig and Gogela, 1949; Henderson, 1973; Reese, 1976).

The relative incidence of this tumour in the first 2 decades has been brought into question by the report by Karp *et al.* (1974) from the Armed Forces Institute of Pathology. This was a multicentric series between the years 1925 and 1968. Twenty-five patients were considered to have a meningioma arising from the optic nerve. Ten patients (40%) were younger than 20 years and 6 (24%) were less than 10 years of age. They concluded that primary intraorbital meningiomas are less rare in children than has generally been assumed and that their data supported the suggestion by Walsh (1975) that primary orbital meningiomas in childhood are more aggressive than those seen in adult life. The case material for this study was a clinicopathological audit extended over a 43-year period.

From the data published in this paper it is apparent that great reliance was placed on the histopathological interpretation of excised tissue. This could well cause errors, for the clinical details were provided by clinicians remote from the laboratory and in many cases well before the advent of sophisticated methods of investigation such as computerised tomographic scanning and ultrasound. The case reported in our communication has shown that the differentiation between gliomas and optic nerve meningiomas cannot rest on histopathology in isolation. We would therefore suggest that the results published by Karp *et al.* (1974) may be incorrect and that some of their cases in the younger age group were in reality gliomas. Certainly the disparity between their figures and those published from this hospital (Wright, 1976) and by other authors (Craig and Gogela, 1949; Henderson, 1973; Reese, 1976) can be explained on this basis.

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British Journal of Ophthalmology, 1979, **63**, 600–606

Clinical presentation and management of lacrimal gland tumours

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SUMMARY This paper presents the clinical and pathological findings in 40 consecutive patients seen with primary tumours arising from the lacrimal gland. Twenty patients had a benign mixed-cell tumour. They presented in a recognisable clinical manner with a painless mass in the region of the lacrimal gland which slowly enlarged over a period of at least 1 year before consultation. Twenty patients had a carcinoma of the lacrimal gland. They had a short history and experienced pain. On clinical grounds they could not be distinguished from inflammatory lesions in the region of the lacrimal gland. The method of treating these 2 groups of patients is described and methods of dealing logically with their problems are suggested.

This communication presents an analysis of the mode of clinical presentation of a large series of lacrimal gland tumours. The correct management of lacrimal fossa lesions depends on recognising the characteristic clinical presentation of benign mixed cell tumours so that a biopsy is avoided and the capsule of the tumour remains intact. Excision of the whole of the lacrimal gland together with the tumour avoids any risk of seeding tumour cells into the adjacent tissues with the possibility of a recurrence with malignant potential (Rubin, 1947; Zimmerman *et al.*, 1962; Waller *et al.*, 1973).

All other lesions in this region, apart from acute dacryoadenitis and dermoid cysts, require incisional biopsy through an anterior approach so that a definitive histological diagnosis can be made. After such a biopsy histological as well as clinical criteria can be used to decide which type of treatment is most appropriate.

Material and methods

Clinical records and histopathological findings of 108 patients with lesions of the fossa of the lacrimal gland seen in the Orbital Clinic at Moorfields Eye Hospital, London, from 1968 to 1979 were reviewed in an attempt to identify clinical characteristics that would allow recognition of benign mixed lacrimal gland tumours from other lesions of the superotemporal orbit. There were 40 cases of benign or malignant epithelial lacrimal gland tumours. All had plain radiographs and a histological diagnosis. The other cases were nonepithelial lesions such as acute and chronic nongranulomatous inflammation, granulomatous inflammation, ideopathic inflammatory pseudotumour, lymphoma, and dermoid cysts. Orbital involvement in some of these cases was not confined to the lacrimal fossa.

Evaluation of patients presenting with lacrimal gland fossa symptoms and signs included a general medical examination, blood studies, and plain and tomographic radiographs of the orbits. Orbital ultrasonography and computerised tomography were performed in selected cases.

Results

Twenty patients in the series had benign mixed lacrimal gland tumours. They comprised 11 men and 9 women, with an age range of 21–68 years (Table 1). The duration of symptoms was greater than 1 year in 19 patients, only 1 patient with a benign mixed tumour had pain. Radiological abnormalities were seen in 18 patients; all had enlargement of the lacrimal gland fossa due to pressure erosion of the overlying bone. Occasionally this erosion was sufficient to breach the orbital wall, with exposure of the dura of the anterior cranial fossa. In addition sclerosis of bone was

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Table 1 *Clinical details of 40 patients with lacrimal gland tumours*

Age (years)	*Benign mixed cell lacrimal gland tumours (20)*	*Malignant epithelial tumours (20)*		
		Malignant mixed cell tumours (2)	*Adenocystic carcinomas (9)*	*Other carcinomas (9)*
0–	–	1	2	1
20–	3	1	1	1
30–	5	–	2	–
40–	6	–	1	1
50–	5	–	2	2
60–	1	–	1	4
70+	–	–	–	–
Sex				
M	11	–	4	5
F	9	2	5	4
Duration of symptoms (months)				
0–	–	–	–	–
3–	–	1	3	3
6–	–	–	1	2
9–	1	–	2	3
12–	3	–	2	1
18–	16	1	1	–
Pain				
Present	1	1	8	6
Not present	19	1	1	3
X-*ray findings (plain and tomographic)*				
Normal	2	–	2	1
Pressure	18	2	6	5
Destruction	–	–	1	3

present in 1 patient in association with pressure changes.

Malignant neoplasms accounted for 20 of the 40 patients with primary epithelial tumours originating in the lacrimal gland. There were 9 adenoid cystic carcinomas, 2 malignant mixed cell tumours, and 9 carcinomas of other types. There was a wide age distribution. It was noteworthy that 7 patients were under 30 years of age, and 4 of the 7 had been treated elsewhere for suspected orbital cellulitis. Fifteen patients had had symptoms for less than 1 year. Only 1 of the patients with a history of longer than 12 months had an operable tumour. This was a case of carcinomatous change in a pre-existing benign mixed tumour. Fifteen patients had noticed pain, and 3 of these patients had associated loss of sensation in the distribution of the frontal nerve. Radiological changes were encountered in 17 patients. Thirteen showed a pressure erosion of overlying bone; 4 patients had demonstrable destructive changes in adjacent bone on plain or tomographic views. Of the 13 patients with pressure changes, 3 had calcification within the lacrimal gland, and 2 had sclerotic changes in the bone adjacent to the expanding lacrimal fossa.

Nine of the malignant neoplasms were considered inoperable at the time of presentation at Moorfields Eye Hospital, either because of extensive involvement of bone or evidence of spread beyond the limits of even the most extensive surgical approach. All the cases in which tumour had spread beyond potential surgical margins had an interval from their initial presentation to an outside ophthalmic service until referral and/or definitive tissue diagnosis of greater than 3 months. The average interval was 4 months. For those patients who had resectable tumours the interval was only 2 months.

The nonepithelial lesions in the review included acute dacryoadenitis, idiopathic inflammatory pseudotumours, and lymphomatous lesions. These lesions represent a broad and varied spectrum of clinical presentation. Ages ranged from the first to the eighth decades. The duration of symptoms was generally less than 6 months. Inflammatory signs and discomfort were relatively common. *X*-ray abnormalities were most unusual.

Discussion

It is essential when dealing with lesions of the lacrimal gland that a neoplasm arising from the epithelium of the gland is recognised as soon as possible. The survival of the patient depends on the correct choice of treatment for the lesion. Analysis of cases presented in this communication has shown that, while carcinomas of the lacrimal gland cannot be distinguished from other rapidly expanding lesions in this region other than by histological examination, benign mixed-cell tumours can be readily recognised on clinical grounds.

The pattern of presentation of benign mixed lacrimal gland tumours is characteristic. They present in patients in their late 20s to early 60s with a slowly progressive painless swelling in the upper lid without inflammatory symptoms or signs. A palpable mass is often in the upper temporal quadrant of the orbit (Fig. 1). A careful detailed history will reveal that the duration of symptoms is more than 12 months. Radiographs usually show enlargement of the lacrimal fossa without invasion of overlying bone (Fig. 2) (Jones and Pfeiffer, 1954; Newton, 1962; Lloyd, 1975). Careful tomographic study may disclose this characteristic change when plain x-rays are negative (this occurred in 1 patient in our series). Coronal computerised tomography (CT) scans will confirm the presence and extent of the tumour (Fig. 3). Although the clinical presentation of cases of benign mixed lacrimal gland tumours has been described in a number of excellent reviews (Forrest, 1954; Davies, 1954; Reese, 1956; Zimmerman *et al.*, 1962; Henderson, 1973), the characteristic clinical presentation of these tumours has not been fully recognised.

Occasionally a benign mixed lacrimal gland tumour may present in a different way. The patient gives a short history, there is a readily palpable mass, and radiographs are normal. This tumour arises from the palpebral lobe of the lacrimal gland and produces a slowly enlarging mass in the outer third of the upper eyelid. In this situation the mass is noticed at an early stage, and because it lies anterior to the lacrimal fossa there is no bone erosion. Inevitably the mass is either biopsied or removed and the true nature of the lesion discovered by frozen section or routine histology. One such case is included in this communication.

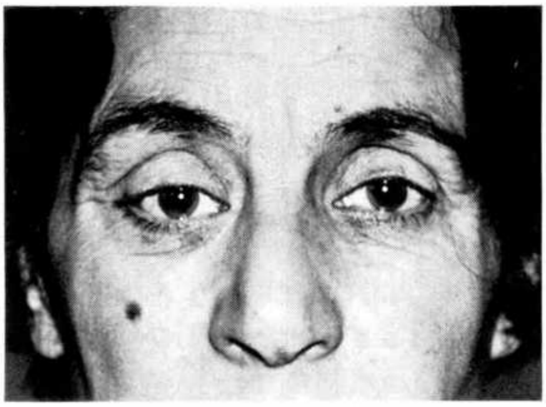

Fig. 1 *Patient with benign mixed cell tumour in right orbit. Fullness of the right upper eyelid and proptosis noticed for 18 months*

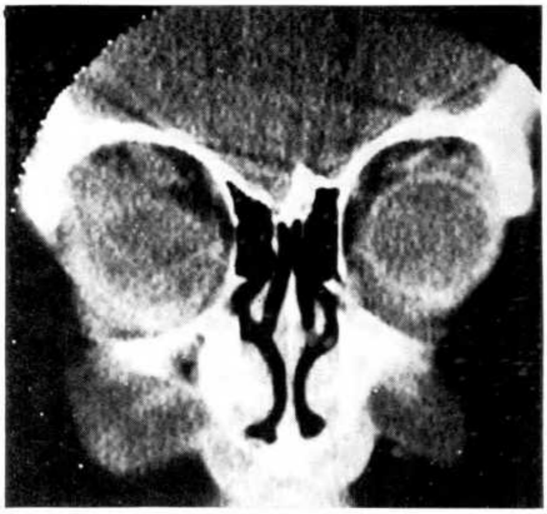

Fig. 3 *Coronal CT scan demonstrating benign mixed cell tumour of the right lacrimal gland causing downward displacement of the globe*

Malignant tumours arising from the lacrimal gland in our series had 2 characteristic features—a short history with a rapidly worsening course and pain (Fig. 4). Both these features have been noted before. Two-thirds of the patients in Zimmerman's series with carcinoma unrelated to mixed tumours had symptoms of less than 9 months when they first

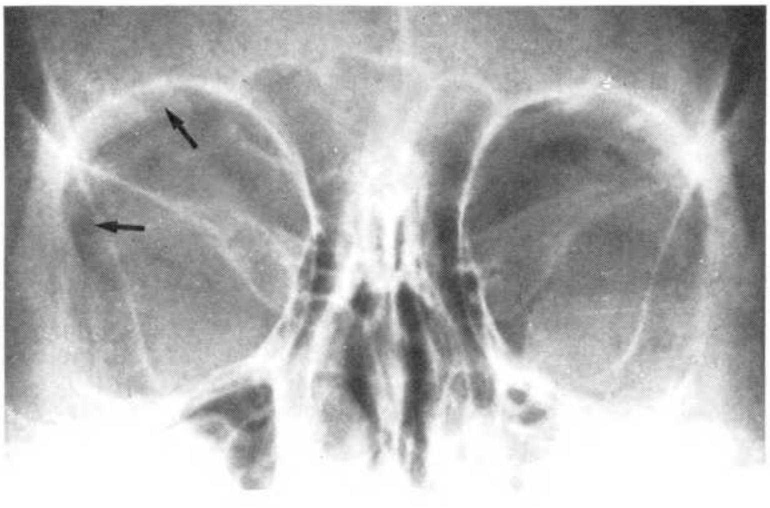

Fig. 2 *Plain radiograph of orbits showing expansion of right lacrimal fossa (arrowed) produced by the slow growth of the benign mixed tumour*

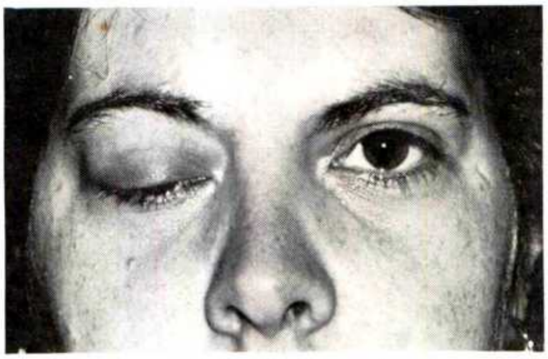

Fig. 4 *Patient aged 31 with an adenoid cystic carcinoma. Painful mass for 6 months*

presented with orbital complaints. The tendency for patients with malignant tumours to experience pain in a high percentage of patients was also noted by Zimmerman and Forrest. Radiographic findings may also help in distinguishing between the malignant and benign lacrimal gland tumour. Carcinomatous lesions often enlarge so rapidly that radiographs in the early stages are normal. Later, enlargement of the lacrimal fossa, with or without demonstrable invasion of bone, may be seen. In 3 patients calcification within the malignant tumour was demonstrated (Fig. 5). In all such patients it is important that both axial and coronal tomograms are obtained so that the structure of the bones in relation to the tumour can be examined in some detail. This type of assessment has now been supplemented by coronal and axial CT scans. Thus an overall picture of the extent of the lesion can be made.

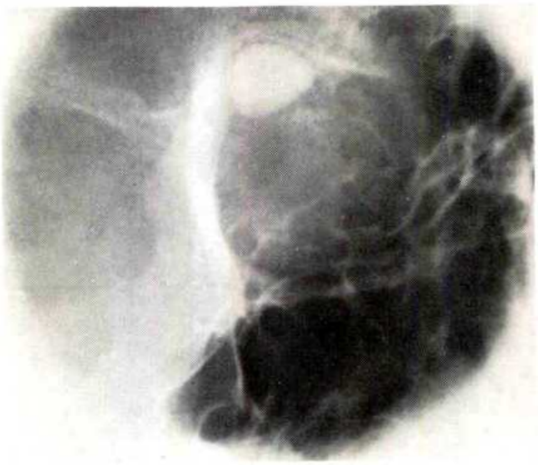

Fig. 5 *Oblique radiograph of right orbit showing expansion of the lacrimal fossa by a partially calcified adenoid cystic carcinoma*

Other lesions affecting the lacrimal fossa must be considered in the differential diagnosis. Acute dacryoadenitis, although described by Duke-Elder and MacFaul (1974) as a rare entity, occurs fairly frequently. Patients present with a short history measured in days rather than months. The upper lid is red, swollen, and extremely tender, and there is usually some conjunctival chemosis with an associated purulent discharge. The preauricular and cervical nodes are often enlarged and the patient pyrexial. Radiographs are invariably normal, and blood studies frequently reveal a raised white cell count. This type of dacryoadenitis should settle rapidly with appropriate systemic antibiotic therapy. Secondary dacryoadenitis related to mumps, infectious mononucleosis, or herpes zoster does not respond to antibiotic therapy and is usually seen in association with characteristic systemic abnormalities. Chronic dacryoadenitis may follow acute inflammation or be due to sarcoidosis or some of the odd inflammatory reactions which merge into the pseudotumour group. It is this group of patients who are difficult to distinguish from those with early malignant tumours arising from the lacrimal gland.

Inflammatory pseudotumours in the region of the lacrimal gland are relatively common. Although they are rare in the very young, the age variation is wide (Chavis *et al.*, 1978). Most commonly the signs and symptoms are similar to those seen in acute dacryoadenitis, though the patient is apyrexial with a normal white cell count. Some patients have a slowly enlarging mass which may not be tender, though the pain is frequently noticed. Plain radiographs are invariably normal, and CT scans will demonstrate the size and extent of the mass. Ultrasonic scans can provide useful information, the pattern of echoes placing the tumour in the lymphoma-pseudotumour group.

Lymphomatous lesions include a broad spectrum from reactive lymphoid hyperplasia to malignant lymphomas of various types. They most commonly occur in adults with a progressive swelling of the eyelid over a period of several months. Inflammatory signs and symptoms are extremely uncommon. A firm nontender mass can usually be palpated in the region of the lacrimal gland. The presence of a purple pink fleshy lesion underneath the conjunctiva of the upper fornix is characteristic of this lesion. The results of investigations are similar to those seen in inflammatory pseudotumours.

Dermoid cysts may also occur in the region of the lacrimal gland and cause some confusion. Peak incidence is in the first decade. Characteristically, a smooth mass may be palpated in the upper outer quadrant of the orbit, but in some cases the cyst may lie deeply within the orbit, and the only abnormal physical sign is proptosis. The patients present with a swelling of the upper eyelid or with progressive proptosis. On rare occasions the cyst may become inflamed and produce a similar clinical picture to acute dacryoadenitis. Plain radiographs provide the diagnosis. A sharply defined cyst-like bone defect, sometimes with sclerotic margins, is characteristic. Benign mixed tumours and some malignant lacrimal tumours cause a more generalised expansion of the lacrimal fossa. An invasive carcinoma will produce an ill-defined osteolysis quite unlike the picture of a dermoid. CT scans frequently aid the diagnosis by revealing the cystic nature of the lesion and in some cases a fluid level within the cyst produced by sebaceous material and lipid. Ultrasonic scans should also show the cyst, so that in most cases a preoperative diagnosis is correctly made.

Patients with lacrimal fossa lesions can be conveniently divided into 2 groups on clinical grounds. The first group are patients with a suspected benign mixed tumour which is confined to the lacrimal fossa. These patients have a history of longer than 12 months, radiographic evidence of expansion of the lacrimal fossa, and no history of pain. The second group comprises patients with a variety of lesions, lacrimal gland carcinomas, lymphomas, pseudotumour, and other inflammatory lesions. They have a short history, often with pain, and may or may not have abnormal radiographs.

The importance of recognising the first group on clinical grounds cannot be emphasised too often. The temptation to biopsy the lesion should be avoided, and total removal of the whole of the lacrimal gland through a lateral orbitotomy can be planned. The choice of approach to the gland is of prime importance, for the exposure should be such that the palpebral lobe and the structures of the eyelid can be dissected out under an operating microscope. It is essential that in removing the lacrimal gland plus tumour the capsule of the tumour is not touched and that periosteum overlying the tumour is removed at the same time. The modified lateral orbitotomy approach offers the only way to achieve the correct and adequate removal of the tumour. A transcranial anterior orbitotomy or the Berke lateral orbitotomy makes it extremely difficult or impossible to avoid a subtotal or piecemeal removal of the gland and tumour.

Rupture of the capsule of a benign mixed cell tumour affects the prognosis adversely because of seeding of the tumour cells into the surrounding tissues. Recurrences are thus inevitable, and in many cases, although such recurrences are histologically nonmalignant, malignant changes can occur. In patients in whom the recurrences remain benign the outcome is often indistinguishable from that seen in a true carcinoma. The tumour cells invade the apex of the orbit and the surrounding bone. A painful and lingering death ensues, for in most cases the tumour spreads beyond the line of surgical resection, and, although radiotherapy may be used as a palliative measure, benign mixed cell tumours are relatively radioresistant.

Patients with a very short history of a lacrimal fossa swelling and associated inflammatory signs can reasonably be treated with a short course of antibiotics. Resolution within 2 to 3 weeks would be the expected course. Unless the mass shows a progressive decrease in size, early incisional biopsy should be done. Patients with a history of a few months' swelling in the region of the lacrimal gland with or without inflammatory signs or abnormal *x*-rays should be biopsied forthwith.

One other group of patients can be identified in whom an early biopsy is indicated. These are patients who have a history of longer than 12 months but do not fit into the clinical pattern presented by the benign mixed cell tumours. They often complain of pain and show radiological evidence of invasion of the overlying bone or evidence of calcification within the tumour. A biopsy should be obtained in all these cases through a transseptal incision. The extraperiosteal approach should never be used, for the integrity of the periosteal barrier must be maintained to prevent possible seeding of the extraperiosteal space by malignant cells. By following this regimen a definite diagnosis will be reached at an early stage in the clinical evaluation. Such diverse lesions as inflammatory masses, lymphomas, and carcinomas will be accurately identified and the appropriate treatment started.

Patients found to have adenoid cystic carcinomas and other malignant epithelial neoplasms should be evaluated to determine the extent of the tumour. Where there is evidence of restriction of the tumour mass within the periosteal barrier and without involvement of the orbital apex, a radical resection of the area can be undertaken. The skills of a neurosurgeon and plastic surgeon as well as the of ophthalmic surgeon should be united in such a surgical operation. Surgical resection in these cases should include portions of the lateral and superior orbital walls as well as removal of the lids and orbital contents. A report describing the criteria of operability, recommended surgical approaches, and the results of the experience with malignant lacrimal gland neoplasms at Moorfields Eye Hospital is in

Table 2 *Flowsheet of management of lacrimal gland/fossa masses based on duration of symptoms and radiographic findings*

	Duration of symptoms	*X-ray findings*		*Biopsy techniques*				
Lacrimal gland/fossa mass	Short	Normal	With inflammatory signs	2–3 Weeks antibiotic treatment	Improved without mass			
					Improved, unimproved with mass	Observe for regression of mass	With regression	
							Without regression	Incisional biopsy
			Without inflammatory signs	Incisional biopsy				
		Abnormal	Pressure changes	Incisional biopsy				
			Destructive changes	Incisional biopsy				
	Long	Normal		En bloc excisional biopsy				
		Abnormal	Pressure* changes	En bloc excisional biopsy				
			Destructive changes	Incisional biopsy				

Short = duration less than 12 months. Long = duration greater than 12 months. Incisional biopsies done via trans-septal approach. En bloc excisional biopsy done via lateral orbitotomy.
*Characteristic presentation of benign mixed cell lacrimal gland tumour.

preparation. Radiotherapy and chemotherapy may be considered in those cases in which spread has occurred beyond even these wide surgical margins. The outlook for these patients is extremely poor (Forrest, 1954; Zimmerman *et al.*, 1962; Forrest, 1971; Henderson, 1973; Ashton, 1975).

This approach, graphically summarised in Table 2, diminishes the need for histological diagnosis by frozen section and permits decisions on extensive surgical removal of a neoplastic lesion to be based on evaluation of permanent appropriately fixed and stained microscopic sections. Furthermore, the risks of incisional biopsy of a benign mixed tumour and its subsequent potential recurrence are minimised. This risk cannot be completely eliminated, for occasionally a patient with a benign mixed-cell tumour arising in the palpebral lobe will present with a short history of a slowly enlarging mass similar to a chalazion, and in these circumstances invariably the lesion is approached directly.

No protocol can provide foolproof solutions to the complex decisions facing the surgeon. Nonetheless, this diagnostic approach based primarily on clinical history and radiographic findings, does provide a logical approach to the problem of lacrimal gland and fossa lesions. In part the dismal prognosis of malignant lacrimal gland tumours is related to delay in diagnosis, with subsequent spread beyond the limits of surgical excision. We think that an improved survival rate can be achieved by an aggressive attitude towards early biopsy followed by extirpative surgery.

Our thanks are due to the various consultant ophthalmic surgeons who referred the cases to the Orbital Clinic, to Dr G. A. S. Lloyd for his help with the interpretation of the radiographs, the Department of Medical Illustration for the preparation of the clinical photographs, and to Mrs S. J. Cole for her assistance in the preparation of the paper.

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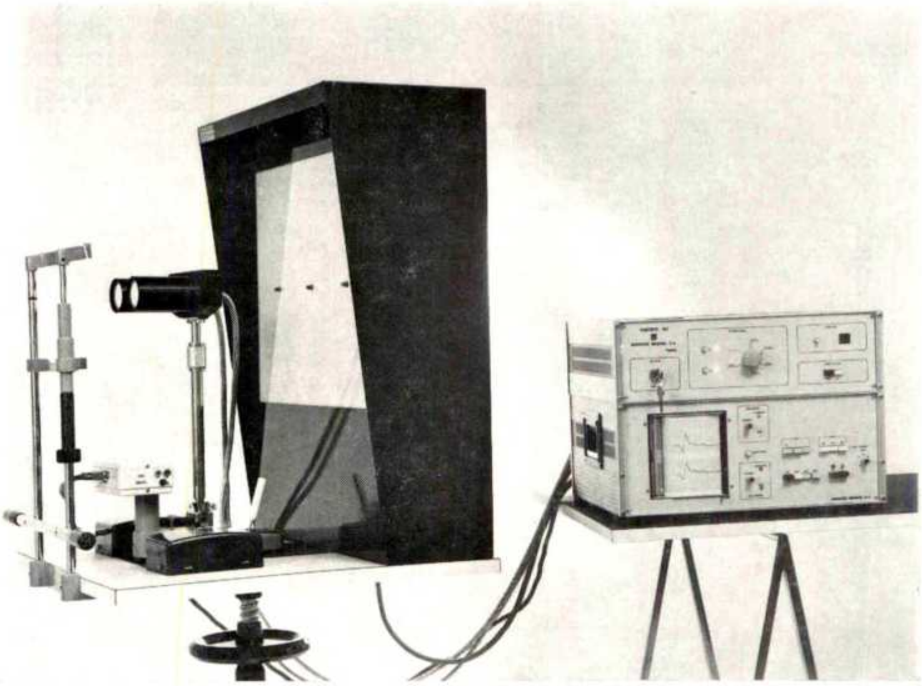

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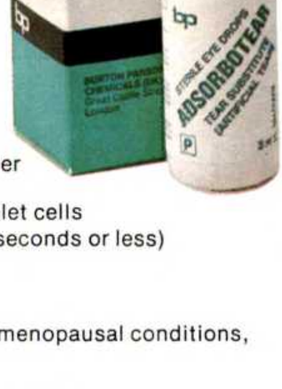

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British Journal of Ophthalmology, 1979, **63**, 607–610

Optic nerve injury in fracture of the canal

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SUMMARY A case of unilateral blindness following blunt injury to the skull is presented. The patient died 4 days after the initial injury, presenting the rare opportunity of a detailed histopathological study of the acute features of the condition. The findings are discussed in the context of current theories of the pathogenesis of optic nerve injury in fractures of the optic canal.

Unilateral visual loss following closed head injury has attracted considerable attention, but this is only in part a reflection of the devastating effect on vision that injury of this type can have. Despite the accumulation of much information the exact pathogenesis of canalicular optic nerve injury remains largely a matter for speculation. The reason for this lies in the very nature of head injury; the patient either survives, allowing only clinical documentation, or dies without regaining consciousness, allowing only histopathological documentation. It is not surprising, therefore, that there is an almost complete absence of material allowing clinicopathological correlation.

The author takes the opportunity of presenting a case of optic nerve injury in which clinicopathological correlation was possible.

Case report

A previously healthy 72-year-old woman was struck by a motor vehicle on the left side of her body and head while crossing the road. She lost consciousness instantly. When she regained full consciousness in the hospital casualty department approximately 30 minutes after the accident she found that the left eye was blind.

A general examination showed multiple skin abrasions on the left side of the body and forehead. There was evidence of a left Pott's fracture and a fracture of the right pubic ramus.

Ophthalmological examination confirmed that there was no perception of light in the left eye. The right vision was 6/6 unaided with a full field. Apart from a discrete subconjunctival haemorrhage there was no evidence of direct injury to the left globe. The orbital margin was intact, and there was no displacement of the globe. Ocular movements were full. There was a complete afferent pupil defect on the left, but a normal consensual reaction. Fundal examination showed a normal optic disc and retina. The central retinal artery pressure appeared normal on digital pressure.

A neurological examination revealed no abnormality. No fracture was seen on plain x-rays of the skull and orbits. A more detailed radiological examination of the orbits and optic canals was not possible owing to her multiple injuries.

On the third day she developed a hypostatic pneumonia and died the following day.

At necropsy the brain showed numerous haemorrhages on the surface of the left cerebral hemisphere. A small linear epidural haematoma indicated an isolated fracture involving the left lesser wing of the sphenoid (Fig. 1). By stripping the dura from the entire cranial cavity it was clear that the fracture did not form part of a larger system of fractures. The left optic nerve appeared grossly intact, but there were scattered superficial haemorrhages where it emerged from the optic canal.

A block of bone, including the posterior segments of both orbits, both optic canals, and both optic nerves and chiasm, was removed in one piece. The specimen was examined macroscopically and it was noted that the fracture extended medially through the body of the sphenoid and involved the posterior part of the left posterior ethmoid sinus.

The entire specimen was fixed in formol saline. In order to complete the radiological examination the fixed specimen was immersed in a saline bath. Plain x-rays of the left optic foramen and horizontal hypocycloidal axial tomography were performed. It was not possible to demonstrate the fracture by either of these methods. The specimen was decalcified and a portion, including the left optic canal and nerve, was embedded in paraffin wax. This was cut into 4 blocks, and sections were cut at various

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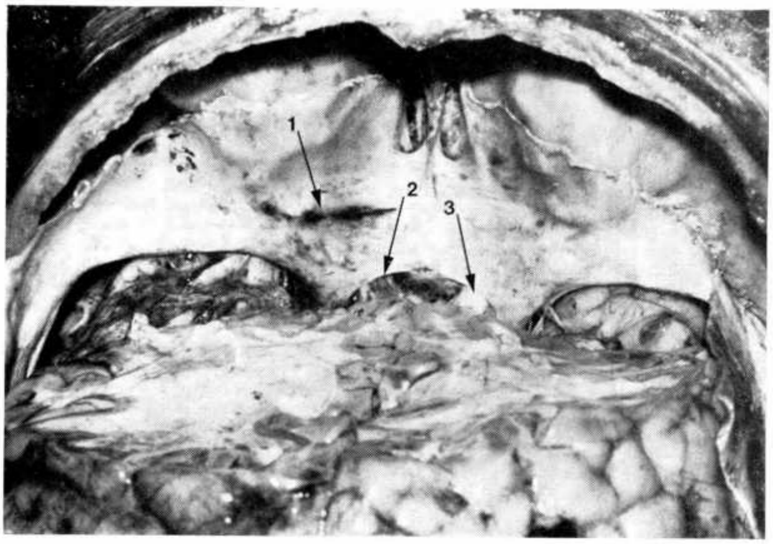

Fig. 1 *Coronal view of anterior cranial fossa.* (1) *Linear epidural haemorrhage marking fracture line.* (2) *Left optic nerve emerging from canal and showing superficial haemorrhages.* (3) *Normal right optic nerve*

levels throughout each block and stained with haematoxylin and eosin.

Microscopic examination showed that in the region of the fracture there was a well localised epidural haemorrhage on the cranial surface of the optic canal. There was only minimal haemorrhage into the dura lining the canal and no gross physical disruption of the sheath or of the nerve in that region. From a level approximately 1 mm anterior to the fracture line and extending posteriorly to about 3 mm posterior to the cranial opening of the canal the nerve was totally infarcted, showing scattered haemorrhages and neutrophil infiltration (Figs. 2, 3). At no level was it possible to identify rupture of small arterioles within the nerve or sheath.

Discussion

Two important points arise from the radiological and histopathological investigations. Firstly, despite the prior knowledge of the position and orientation of the fracture it was not identified by any of the radiological techniques used. Secondly, the absence of physical disruption of the nerve contrasted with its total infarction.

The reported incidence of radiologically identifiable fractures of the optic canal in indirect injuries of the optic nerve varies considerably. Hoffman (1935) identified a fracture in all of an undisclosed number of cases, Rollet (1930) in 80%, Landolt (1955) in 79%, Davidson (1938) in 78%. In contrast Turner (1943), even with special foraminal views, identified a fracture in only 4 out of 37 cases, and Hooper (1951) was unable to detect a fracture in

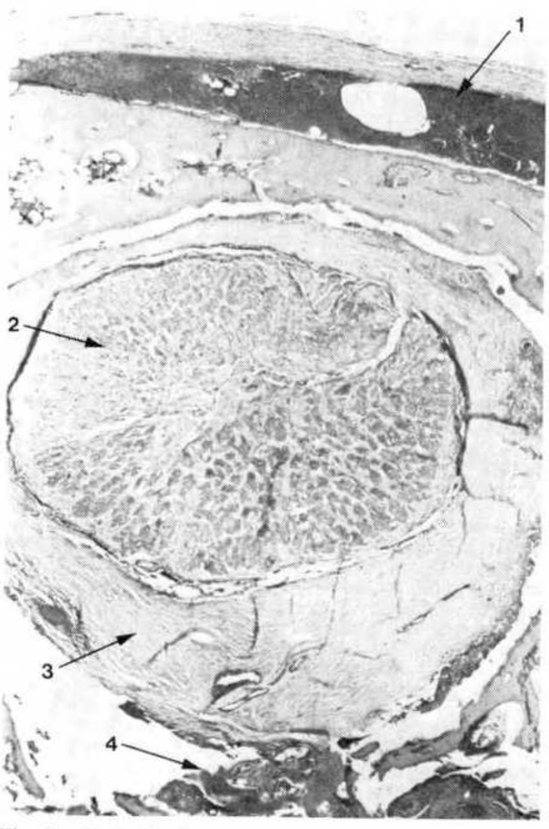

Fig. 2 (1) *Epidural haemorrhage on cranial surface of optic canal.* (2) *Totally infarcted optic nerve.* (3) *Intact sheath.* (4) *Haemorrhage marking fracture site.* ×65

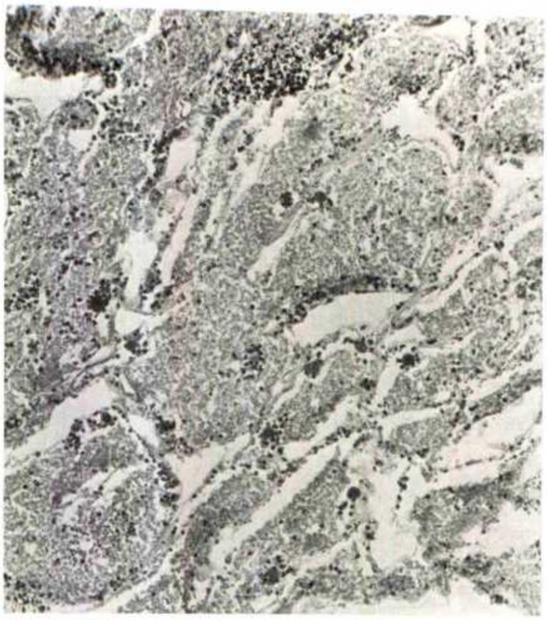

Fig. 3 *High power view of nerve.* × *385*

any of the 24 cases he examined. In a group of 56 cases in which the clinical features strongly suggested a canalicular optic nerve injury Hughes (1962) was able to detect a fracture of the optic canal in only 6%.

Evidence that fractures of the canal may exist where they cannot be detected radiologically comes in reports of cases of late callus formation (Lillie and Adson, 1934) and from the relatively few cases that come to surgery. Lazorthes quoted in Hotte (1970) noticed 2 previously undetected fractures out of 6 cases and Imachi (1967) 16 out of 80 cases.

In the case described the inability to detect the fracture even tomographically with prior knowledge of the position and orientation of the fracture serves to underline the unreliability of radiographical evidence.

In a post-mortem study of 70 patients who died from head injury Walsh and Lindenberg (1963) described lesions of the optic nerves ranging from haemorrhages into the nerve and sheath and oedema of the nerve to contusion necrosis and infarction. They felt that primary contusion necrosis, which they believed resulted from the shearing force on the nerve, and secondary localised necrosis (resulting from damage to small nutrient vessels in the canalicular and intracranial portion of the optic nerve) were of prime importance.

In a review of the clinical, operative and post mortem features of 90 cases of optic nerve injury observed personally Hughes (1962) described 56 cases in which there was evidence of optic nerve injury in the absence of evidence of damage to the chiasm or to the central retinal arterial circulation. These he described as 'canalicular optic nerve injuries', though clearly injuries causing severance of nerve fibres at the point of emergence of the nerve into the cranial cavity as described by Seitz (1963) must also fall into this group. Of these cases those that showed some recovery of vision tended to show altitudinal hemianopias. Similar field defects were also found among 78 cases described by Otradovec (1968). Hughes considered that an altitudinal hemianopia was evidence of a vascular aetiology, as such defects were 'found almost exclusively in vascular lesions of the optic nerve following gastrointestinal haemorrhage, thrombosis in tumours and arteriosclerotic optic atrophy.' However, it should be said that the majority of 'vascular' optic nerve lesions occur around the optic nerve head, a region of the nerve with a blood supply not typical of the rest of the nerve (Hayreh, 1974). In Hughes's series only 2 cases of suspected canalicular optic nerve injury were examined histologically. In neither case had there been any recovery of vision. One was explored 10 days after the injury, and, although the intracranial and posterior orbital portions of the nerve appeared normal, on deroofing the canal a portion of the nerve was found to be completely replaced by debris and blood clot. Unfortunately it is not clear whether there was evidence of optic canal fracture. In the second case examined at necropsy 21 days after the injury there was a fracture of the anterior fossa isolating the optic canal and anterior clinoid. The nerve showed no external abnormalities. In both cases microscopic examination showed a complete infarction of the nerve. Hughes concludes that it is insufficient to explain canalicular optic nerve injury in the majority of cases simply on the basis of the physical injury to the nerve at the fracture site, though clearly such injury can occur. Like Walsh, Hughes suggests that the vessels supplying the nerve within the canal are damaged, so that all or part of the nerve is deprived of its blood supply.

In the case described in this paper the infarction of the nerve might have arisen in 2 ways. The shearing force at the fracture site might have caused the rupture of a small arteriole supplying the nerve, resulting in the infarction of a segment of the nerve, the consequent haemorrhage and oedema in that area compressing the nerve within the canal and causing an extension of the infarction to involve the whole of the nerve. Alternatively, the shearing force, although insufficient to cause physical disruption of the nerve or sheath, might result in oedema nd precipitate the infarction through compression.

In the sections examined no evidence was found suggesting the rupture of a feeder arteriole in the region of the fracture. It seems more likely, therefore, that in the case under consideration the infarction resulted from the compressive effect of a generalised oedema of the nerve and sheath in the region of the fracture. The fact that the area of the infarction of the nerve extended posteriorly from the fracture site for a far greater distance than it did anteriorly can be explained in terms of the blood supply to the canalicular portion of the optic nerve. Steele and Blunt (1956), Hayreh (1962), and François and Fryczkowski (1978) demonstrated in post-mortem specimens that the canalicular portion of the optic nerve was supplied by a variable number of collateral pial branches arising from the ophthalmic artery within the orbit. These vessels or their branches could thus be compressed as they passed posteriorly through the region of the fracture.

In the case presented it is not possible to decide whether the shearing force of the initial injury caused some axoplasmic disruption, which by itself would have been sufficient to cause a complete loss of vision, independent of the effect of the infarction. In those cases where a return of vision is recorded following a radiologically identifiable fracture it is possible that the oedema at the fracture site was insufficient to trigger the infarction of the *entire* nerve and that the initial visual loss reflected a degree of axoplasmic disruption. It is difficult to see how this theory can be put to the test until the opportunity arises to study further cases similar to the one described but in which there was a return of vision before death.

I am greatly indebted to Dr R. D. Hoare, of Guy's Hospital, and Dr G. A. S. Lloyd, of Moorfields Eye Hospital, for their advice in planning the post-mortem radiology and for their interpretation of the films, and to Dr D. R. Turner, of Guy's Hospital, for his help in the preparation and interpretation of the histological sections.

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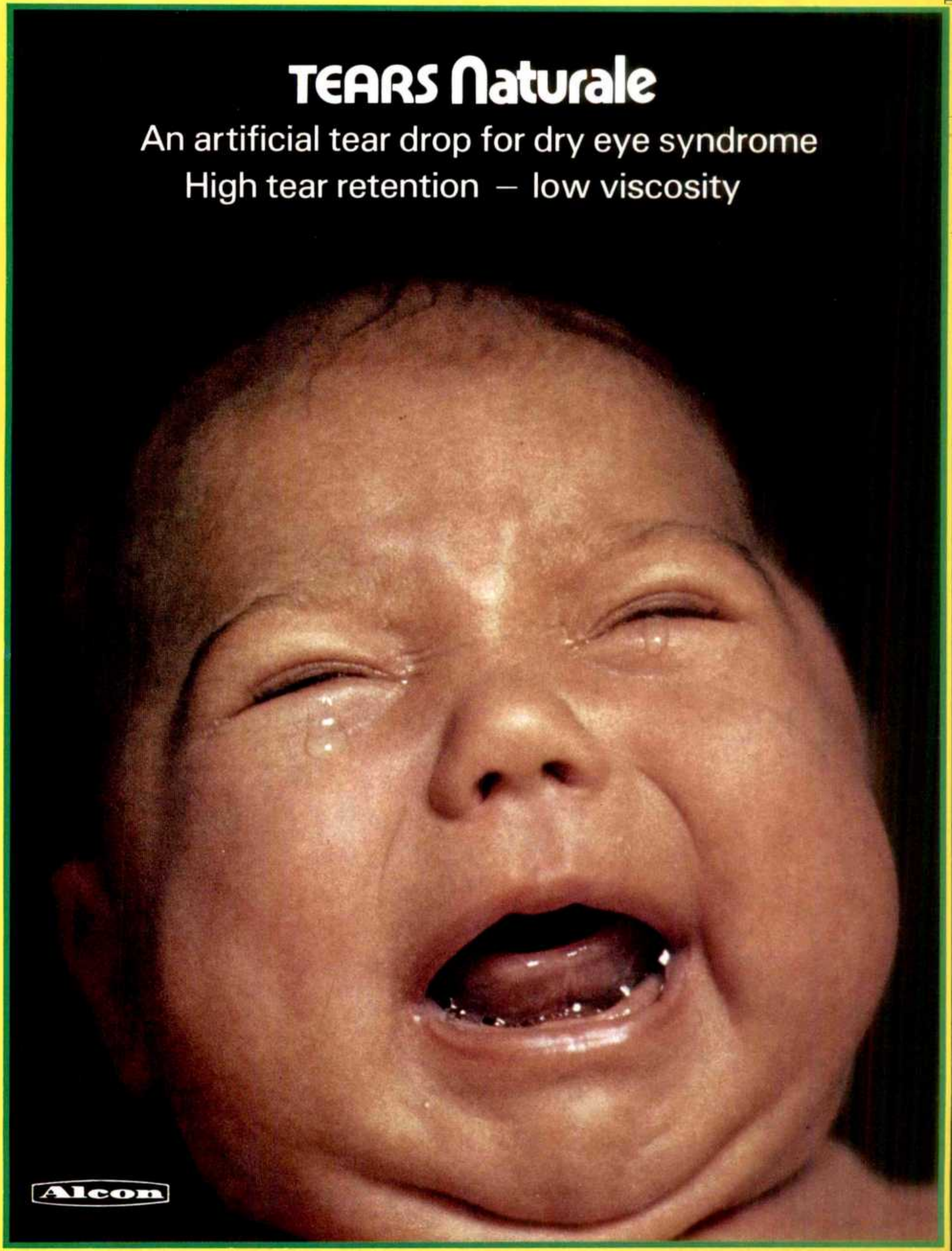
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British Journal of Ophthalmology, 1979, **63**, 611–616

Ocular complications in craniofacial fibrous dysplasia

G. M. LIAKOS, C. B. WALKER, AND J. A. S. CARRUTH

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SUMMARY Three cases of craniofacial fibrous dysplasia are reported, all presenting to the ophthalmologist first. They all had ocular complications due either to direct involvement of the orbital bones or to secondary complications. Sphenoidal mucocele is added to the other complications previously reported, and accordingly a classification of the various ways that fibrous dysplasia can affect the ocular structures is proposed.

Fibrous dysplasia of the bone is a well documented disease that may affect any part of the skeletal system. The aetiology is unknown, but it is probably a developmental mesodermal disorder which may be triggered by trauma (Rees, 1976). The cavity of the affected bone is filled by fibrous tissue that may contain foci of calcified bone, hyalin, cartilage, cysts, and giant cells (Hutter *et al.*, 1963). As a consequence there is diffuse thickening of the affected bones and encroachment on adjacent organs. The radiological appearance is usually typical, but the importance of adequate biopsy is emphasised by the erroneous diagnosis in 25 of 90 reviewed cases by Harris *et al.* (1949). The differential diagnosis should include Paget's disease, osteopetrosis of Albers-Schönberg, and osteogenic sarcoma.

The disease is of particular interest to the ophthalmologist because it can affect the craniofacial bones either as a monostotic fibrous dysplasia or as a part of polyostotic fibrous dysplasia which is sometimes associated with skin pigmentation and endocrine disorders (Albright's syndrome). When the craniofacial bones are affected, encroachment on the paranasal sinuses, orbit, and foramina of the skull can produce visual loss, proptosis, diplopia, and epiphora (Moore, 1969), which more often than not are the first clinical manifestations of the disease.

In this paper we analyse the clinical and pathological findings in 3 cases of craniofacial dysplasia, all presenting to the ophthalmologist first, but each in a different way.

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Case reports

CASE 1

A 12-year-old white boy presented to the Casualty Department of the Southampton Eye Hospital with the history of having fallen off his bicycle 1 week earlier. There was history of a similar blow on the head when the child was 5 years old, and since then he had a swelling on his left temple. There was no visual loss at any stage, and the general health was excellent.

Examination revealed the presence of left facial asymmetry with a bony swelling over the left frontal bone. The left globe was proptosed and displaced inferolaterally (Fig. 1). Visual acuity without correction in the right eye was 6/5 and in the left 6/4. Pupillary responses were normal in both eyes and fundus examination revealed no abnormality in either eye.

Skull *x*-ray films revealed a smooth, relatively

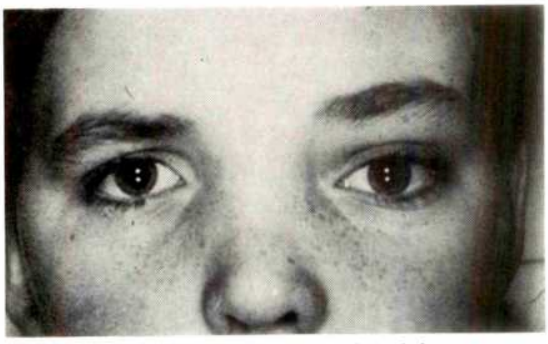

Fig. 1 *Case 1. Note displacement of the left eye inferolaterally*

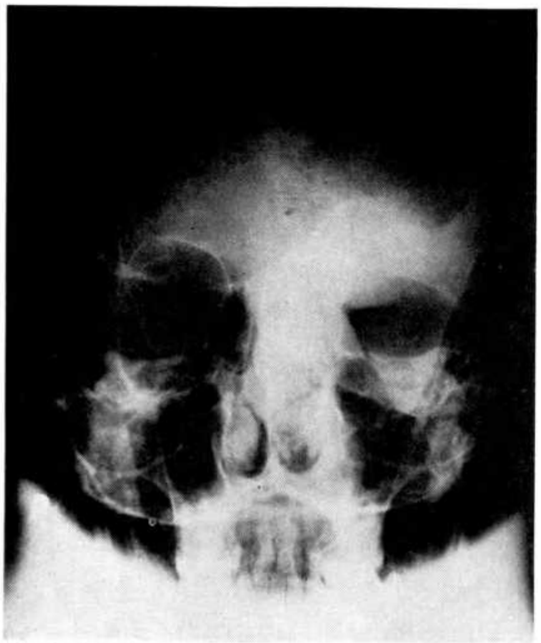

Fig. 2 *Skull x-rays of case 1. Note thickening of bone on the left side, reducing the orbital size*

homogeneous sclerosis and very considerable thickening of the bone on the left side (Fig. 2). This involved the roof of the orbit and extended forwards on to the frontal bone, all of the walls and roof of the maxillary antrum, and the wings of the sphenoid. It had resulted in obliteration of the frontal sinuses, the left ethmoids, and the sphenoid sinus. The left orbit was reduced in size by encroachment, as was the left side of the nasal cavity. The bony thickening also projected upwards into the anterior cranial fossa and the middle cranial fossa. As a result of the clinical and radiological findings a diagnosis of fibrous dysplasia was made.

Tomograms showed that in spite of the dense involvement of the lesser wing of the sphenoid on the left side the optic canal was well shown and appeared to be of normal dimensions.

In view of the unaffected vision, healthy appearance of the optic disc and normal dimensions of the optic canal, a conservative approach was adopted rather than a surgical decompression of the orbit.

Eleven years later, the appearance remains unchanged, with persisting proptosis but normal ophthalmoscopic and radiological findings.

CASE 2

A 31-year-old white man presented to the Casualty Department of the Southampton Eye Hospital complaining of a swelling over his left eye, present for 2 months and rapidly increasing in size. There was some history of trauma 22 years ago when he fell off a tree and suffered head injury. There were no visual complaints, and the general health was excellent.

Examination revealed some facial asymmetry, the bony structure being more prominent on the left side. There was a large mass in the superomedial quadrant of the left orbit displacing the globe inferolaterally (Fig. 3). Despite this there was no diplopia and the extraocular movements were full. Visual acuity without correction in the right eye was 6/5 and in the left 6/6. Fundus examination showed no abnormalities in either eye. Pupillary response to direct and consensual light was normal in both eyes.

Skull *x*-ray films revealed extensive involvement of the whole left side of the head, face, and jaws by fibrous dysplasia (Fig. 4). Every bone on that side

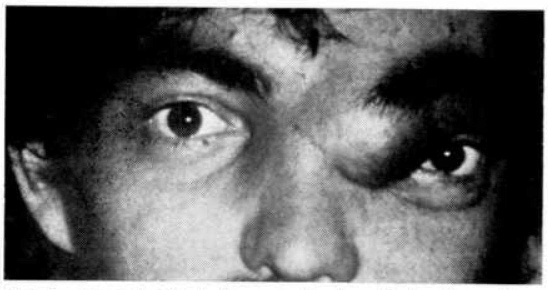

Fig. 3 *Case 2. The left eye is displaced inferolaterally by a large mass in the superomedial quadrant*

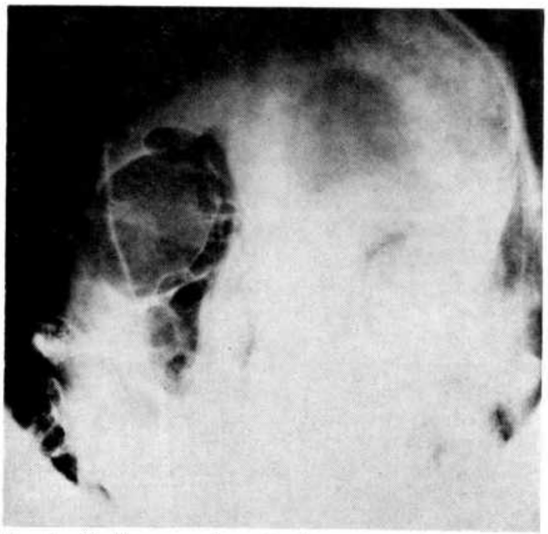

Fig. 4 *Skull x-rays of case 2. The anatomy of the left side is totally disrupted by remarkable thickening of the bones*

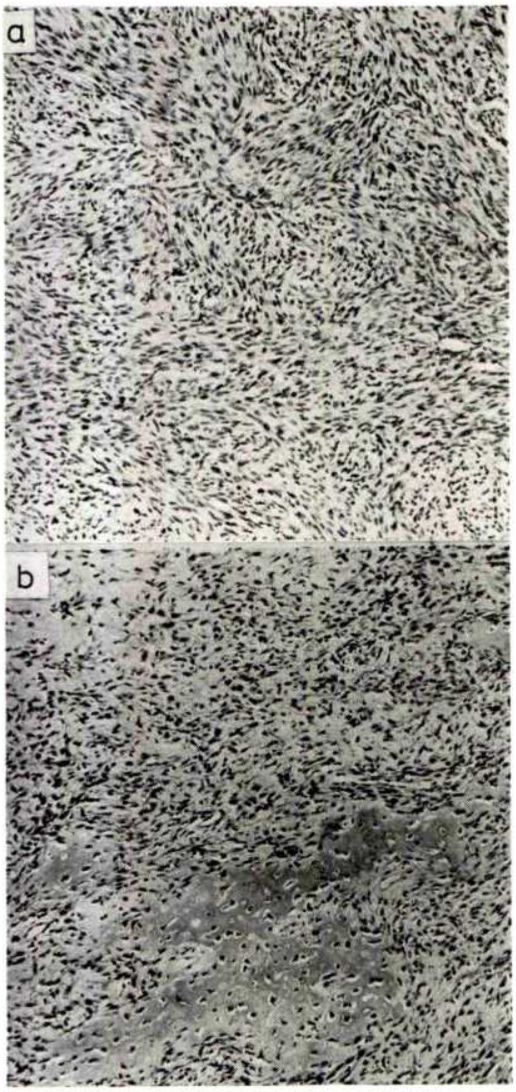

Fig. 5 *Histology of the tumour in case 2.* (a) *Spindle cells arranged into storiform pattern* (*H and E,* ×*80*). (b) *Note formation in parts of cartilage and osteoid* (*H and E,* ×*80*)

of the skull was involved, with remarkable thickening of the body of the sphenoid in particular. The superomedial portion of the left orbit was absent, and there was a 4 mm diameter well-defined lucency contiguous with the left orbit extending into the left frontal bone in the region of the frontal sinus. Chest *x*-ray films revealed fibrous dysplasia of the left 5th, 6th, and 7th ribs.

An orbital tomogram confirmed the presence of an expansile destructive lesion involving the left frontal sinus. It was shown to have eroded the superomedial portion of the left orbit and to have opened into the left frontal fossa. The left maxillary antrum was diminutive, and there was enormous expansion and sclerosis of the sphenoid body and wings on the left side.

At this stage, it was thought that the orbital lesion was a frontal mucocele displacing the globe in the opposite direction, in spite of the rapidity of growth which is uncharacteristic of mucocele. It was only when an anterior orbitotomy was performed that the diagnosis of frontal mucocele proved to be erroneous.

A large nonencapsulated tumour was found instead, occupying the superomedial quadrant of the orbital cavity. The tumour was extending posteriorly and also superiorly invading and totally filling the frontal sinus. Laterally the tumour was free from attachments and was simply pushing the globe, but medially and superiorly it was infiltrating the orbital bones diffusely, hence making the removal difficult and incomplete.

Histological examination revealed the following: Macroscopically a white fleshy tumour 2×3×5 cm. Microscopically a spindle celled tumour, individual cells showing marked polymorphism. There were some individual tumour giant cells with plentiful cytoplasm. In part the spindle cells were arranged into storiform pattern. The mitotic rate was increased (Fig. 5a). Extra and decalcified section of the lesion showed that in parts the tumour cells were forming cartilage and osteoid (Fig. 5b).

CASE 3

A 20-year-old white woman presented to her local ophthalmologist complaining of rapid loss of vision in her left eye and partial loss of vision in her right eye, with normal fundi.

Skull *x*-ray films showed that the left ethmoidal air cells, in particular the posterior group, were dense. There was bulging and destruction of the orbital plate of the left sphenoid bone and of the nasal septum with obliteration of the left nasal air way. Further destruction extended into the basosphenoid across the full extent of the floor of the pituitary fossa. The destruction involved the left optic canal and the medial half of the right optic canal. There was considerable developmental asymmetry of the lesser wing of the sphenoid, and this, together with the bulging of the bone plates, suggested that the lesion may have been slowly growing before its more recent rapid advancement There was no evidence of soft tissue mass in the nasopharynx (Fig. 6).

When she was seen at the Neurosurgical Unit of the Southampton General Hospital, where she was

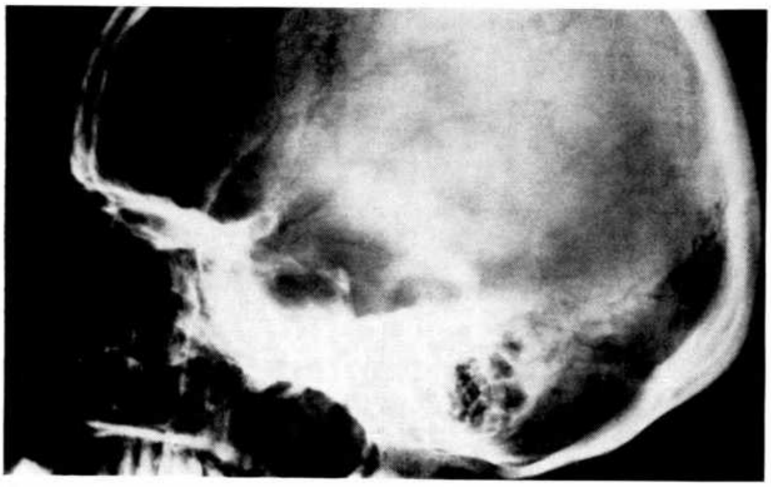

Fig. 6 *Case 3. Destruction of the basosphenoid across the full extent of the floor of the pituitary fossa*

referred, she was totally blind, having no perception of light in either eye. The left eye was slightly proptosed, but the extraocular movements were full. The pupillary reflexes were absent in both eyes, the pupils thus remaining fixed and dilated. Inspection of the fundus confirmed no abnormality. Neurological examination failed to demonstrate involvement of any other cranial nerves.

A CT scan confirmed the obliterations of the left ethmoid sinuses and destruction of the basosphenoid with bulging into the left orbit producing some proptosis and local deformity of the eyeball and deviating the left optic nerve.

At this point it was thought that the lesion was a tumour originating from the ethmoid sinuses and invading the left orbit. Accordingly treatment was introduced by means of local radiotherapy and systemic corticosteroids, but without improvement.

A bone biopsy was done next, which established the diagnosis of fibrous dysplasia (Fig. 7). Very soon after this, bifrontal craniotomy was performed, and confirmed the presence of fibrous dysplasia, mainly centred around the ethmoid and sphenoid sinuses. The most interesting finding, though, was a large mucocele originating from the sphenoid sinus and spreading out on both sides, encircling both optic nerves. Inside the cavity of the mucocele there was an extensive haemorrhage, obviously accounting for the acute visual loss.

Six months after the operation there was no return of visual function, and the discs were pale and atrophic. Skull *x*-rays revealed remarkable reconstitution of the pituitary fossa (Fig. 8).

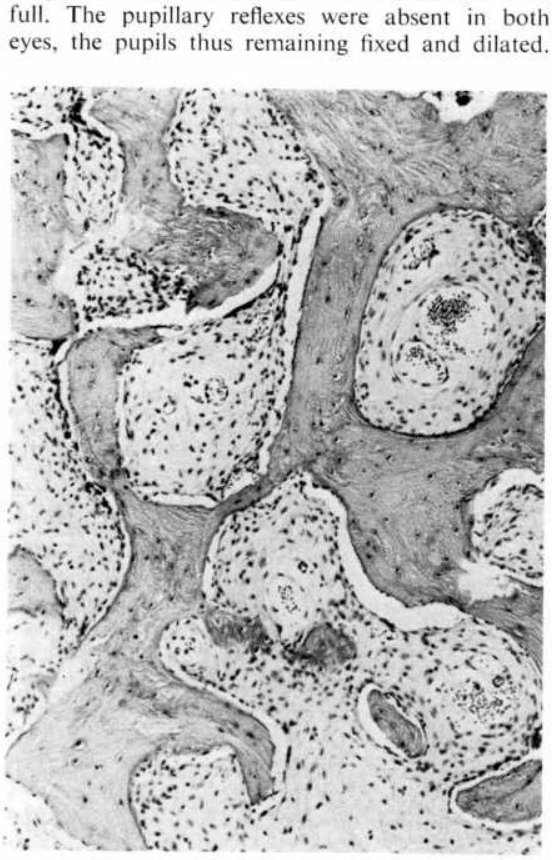

Fig. 7 *Histology of fibrous dysplasia, with fibrous tissue invading the bone (H and E, × 80)*

Discussion

The first case illustrates the typical picture of proptosis due to fibrous dysplasia as described by other authors (Mortada, 1961; Moore, 1969; Gogi *et al.*, 1976; Schonder, 1977; Friot *et al.*, 1978). Every young patient with unilateral proptosis should be investigated for craniofacial fibrous

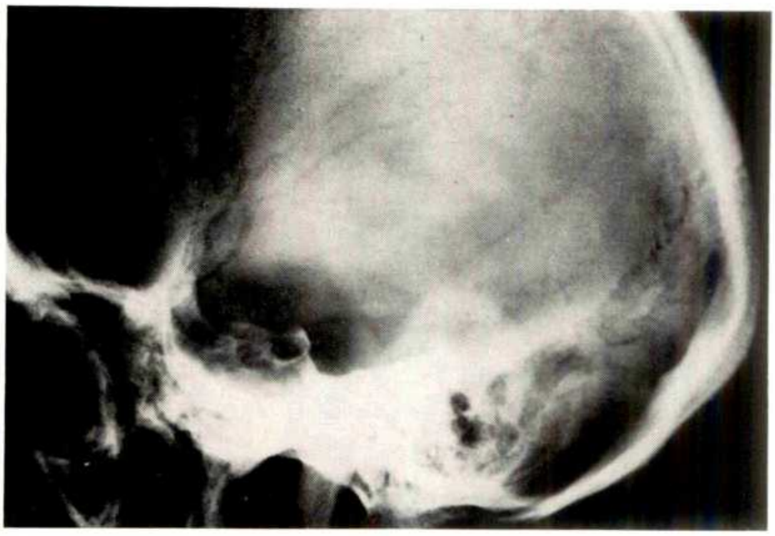

Fig. 8 *Postoperative appearance of case 3. Note remarkable reconstitution of the pituitary fossa and large frontal craniotomy*

dysplasia (Daves *et al.*, 1957; Natchiar, 1976). Radiological screening must include special views of the optic foramina, and surgical intervention is indicated when compression of the optic nerve becomes imminent. Unilateral involvement is the rule, but cases with bilateral visual impairment are found in the literature (Calderon *et al.*, 1969; Sassis *et al.*, 1968). Finney and Roberts (1976) described a case of fibrous dysplasia of the skull that developed trigeminal neuralgia, and we recently saw a case of 6th nerve palsy that was thought to be due to fibrous dysplasia. Thus it seems likely that besides the optic nerve other intracranial nerves can be involved as well.

The commonest complication of fibrous dysplasia is its malignant transformation to osteosarcoma (Coley *et al.*, 1945; Jaffe, 1946; Perkinson and Higgenbotham, 1955; Yannapoulos *et al.*, 1964; Schwartz and Alpert, 1964; Caron *et al.*, 1971), and is demonstrated by the second case of this paper. The most interesting aspect of this case was the histology. Bony formation was scanty for a typical osteosarcoma, and a large amount of fibrous tissue gave the tumour a predominantly fibroblastic appearance. It is known that, histologically, osteosarcoma varies from case to case and from one area to another in the same tumour (Hogan and Zimmerman, 1962), but Jakobiek and Tannenbaum (1974) suggested that the fibroblast occupies a central position in the differentiation of many connective tissue tumours. If this theory is accepted, it is possible that many tumours reported as osteosarcomas because of some osteoid formation in fact arise from fibroblasts, some of which enter into morphological continua with the osteocyte. Two other rare forms of tumours complicating fibrous dysplasia have been reported on the basis of their histological appearance: adamantinoma (Baker *et al.*, 1954) and cutaneous fibromyxoma (Lick and Viehweger, 1962).

The third case of this paper presents an interesting course of events combined with unusual clinical features and findings. Mucocele of the sphenoid sinus is rare (Nugent *et al.*, 1970; McCarthy *et al.*, 1972). Among the many neurological, nasal, and visual symptoms, gradual visual loss is sometimes the only clinical finding, as reported by Stanton (1970). The course is slowly progressive and may mimic pituitary neoplasm (Nevins and Leaver, 1967). Acute visual loss is uncharacteristic, and that renders our case unusual. But what makes our case unique is the presence of fibrous dysplasia, which can undoubtedly be regarded as the original pathology, the mucocele simply representing a complication. To our knowledge sphenoidal mucocele complicating fibrous dysplasia of the craniofacial bones has not been previously reported, although Grimaud *et al.* (1968), in a patient with fibrous dysplasia, described a mass invading the orbit from the frontal sinus, calling it ossifying fibroma, and Silva in the same year presented a similar lesion.

It is clear that fibrous dysplasia affects the ocular structures in many ways, and these are classified as follows:

A. Primary. (1) Frontal bone involvement resulting in proptosis, bony swelling. (2) Base of the skull involvement, resulting in extraocular muscle palsy and trigeminal neuralgia. (3) Optic canal involvement, resulting in visual loss and optic atrophy.

(4) Body of the sphenoid involvement, resulting in chiasmal compression. (5) Maxillary bone involvement, resulting in epiphora.

B. Secondary. (1) Malignant transformation: (*a*) osteosarcoma, (*b*) fibrosarcoma, (*c*) adamantimoma, (*d*) cutaneous fibromyxoma. (2) Mucocele. (3) Ossifying fibroma.

We believe that this comprehensive list includes all the different ways that fibrous dysplasia can produce orbital or ocular symptoms, and can therefore be useful to the ophthalmologist.

We are grateful to Mr Jason Brice and Mr John Whitwell for allowing us to study their case. We should also like to thank Mr F. Sims for the illustrations, and Mrs J. Shapter for secretarial assistance.

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Comparative sensitivity of a cultural test and the complement fixation test in the diagnosis of adenovirus ocular infection

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SUMMARY The sensitivity of human embryonic kidney (HEK) cell culture and the complement fixation test (CFT) in the diagnosis of adenovirus ocular infection has been compared. The optimum time for collection of specimens to obtain the best results by each test has been examined. Sixty-one (53%) of 116 patients with moderate to severe follicular conjunctivitis, clinically indicative of adenovirus infection, had serological evidence of infection or had the virus isolated from ocular swabs. Virus was isolated from 53 patients (45%) and significant antibody rises were found in 33 (27%). When each test was carried out under optimum conditions, virus was isolated from 82% of cases and serological evidence of infection found in 72%. Serological responses as detected by the CFT appeared to be inferior in infections caused by adenovirus type 7 to those encountered in infections due to adenovirus types 3 and 8.

The ocular morbidity associated with adenovirus infections varies considerably. These eye infections constitute a major economic problem owing to the loss of a considerable number of working days each year. Sporadic cases of acute follicular conjunctivitis and keratoconjunctivitis caused by various serotypes of adenovirus are common entities. Adenovirus serotypes 3, 4, 7, 8, and 19 particularly are responsible for outbreaks of the disease in hospitals, factories, and schools (Editorial, 1977).

Several laboratory tests are available for the diagnosis of adenovirus ocular infection. Cell cultures for virus isolation and the complement fixation test (CFT) for detection of antibody to adenovirus group antigen are routine laboratory procedures which are extensively used for the diagnosis of ocular infection.

In this paper we compare the sensitivity of a primary human embryonic kidney (HEK) cell culture system with the complement fixation test for the diagnosis of adenovirus infection of the eye. The optimum time for collection of specimens to obtain the highest positivity rate by each test is discussed.

Materials and methods

SELECTION OF PATIENTS

Patients attending the clinic with moderate to severe follicular conjunctivitis or keratoconjunctivitis clinically suggestive of an adenovirus infection were included in this study.

CULTURAL TEST

Swabbings collected from different areas of the conjunctiva (Darougar and Jones, 1971) were placed in plastic capsules containing 2SP transport medium (Gordon *et al.*, 1969) with additional fetal bovine serum, and stored at –70°C until required.

Each specimen was inoculated into 2 tubes of HEK cells and examined at regular intervals for the presence of cytopathic effect (CPE) for up to 21 days (McSwiggan *et al.*, 1975). The isolates were identified and serotyped by standard methods.

SEROLOGICAL TEST

Serum collected by venepuncture was tested by a complement fixation test (Bradstreet and Taylor,

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1962) for detection of antibody against adenovirus group antigen.

STATISTICS

Results were submitted to statistical tests of significance by the chi-square test.

Results

VIRUS ISOLATION

A total of 125 specimens were collected from 116 patients. Of these, 53 (45%) yielded adenoviruses; the various serotypes isolated are shown in Table 1. The isolation rates in relation to the time of collection of specimens after the onset of symptoms are shown in Fig. 1. Of the specimens collected during the first week of ocular infection 66% (41 out of 62) were positive. The isolation rate dropped to 25% (7 out of 28) for the specimens taken during the second week of infection and fell further to 12% (2 out of 17) in specimens collected during the third and fourth week of infection. Of 18 specimens collected during the second month of infection 3 were positive, 2 yielded adenovirus type 3 (isolated 52 and 58 days after onset), and 1 yielded adenovirus type 8, isolated 50 days after onset.

COMPLEMENT FIXATION TEST

Where 2 or more convalescent sera were available from 1 patient, each was paired with the acute serum separately. This gave a total of 210 paired sera from the 116 patients included in this study. The complement fixation test on these paired sera showed a 4-fold or higher rise in titre of group antibody against adenovirus in 33 (28%) of cases and less than 4-fold or no rise in 34 (29%). In the remaining cases antibody to adenovirus was not detected.

Table 1 *Distribution of adenovirus serotypes among 53 isolates*

Serotype	*Number (%) of isolates*
1	1 (2)
3	16 (30)
4	2 (4)
5	3 (6)
7	12 (23)
8	12 (23)
19	4 (7)
15/29	1 (2)
Untyped	2 (4)

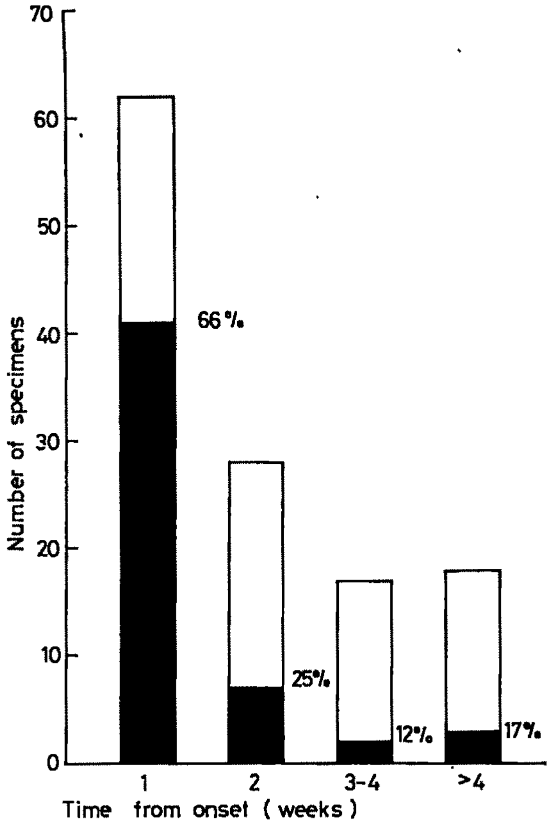

Fig. 1 *Adenovirus isolation rate in relation to the time of collection of specimens after the onset of infection*

The result of antibody tests in relation to the time of collection of acute and convalesent sera from the onset of ocular infection is shown in Fig. 2. When the acute serum was obtained within 1 week and the convalescent serum 3–5 weeks after onset of disease, 16 of the 33 (48%) sets of paired sera showed a significant (4-fold or higher) rise in antibody titre. This figure dropped to 5 out of 27 (19%) when the convalescent serum was not collected until after 5 weeks. When the acute serum was collected during the second week and the convalescent serum within 3–5 weeks of infection, a significant rise in antibody was observed in only 3 out of 20 (15%) sets; this dropped to 4 out of 62 (6%) if the convalescent serum was not obtained until after 5 weeks (Fig. 2).

The serological responses in relation to serotypes of adenovirus were studied in cases where the acute serum was taken during the first week of infection. The results (Table 2) suggest that adenovirus types 3 and 8 tend to produce a higher antibody response

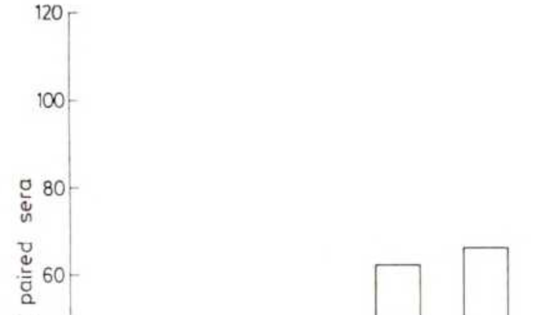

Fig. 2 *Complement fixation positivity rate in relation to the time of collection of sera after the onset of infection*

Table 2 *Serological response in patients infected with different adenovirus serotypes*

Serotype	*Number of cases**	*Number CFT +ve†*
3	13	8
4	1	1
5	2	2
7	8	2
8	8	5
19	3	2
15/29	1	0

*Number of cases in which the first serum was taken at ≤7 days after the onset of symptoms.
†Cases showing four-fold or greater rise in CF titre.

(as detected by CFT) than adenovirus type 7. The number of patients infected with various serotypes of adenovirus was not large enough to allow a valid conclusion.

COMPARATIVE SENSITIVITY OF CULTURAL AND COMPLEMENT FIXATION TESTS

Sixty-one of the 116 patients in this study had evidence of infection with adenoviruses as shown by virus isolation or by antibody tests or both. Cultural test was positive in 53 (45%) and CFT in 33 (27%). This difference between the 2 tests is statistically significant ($P<0\cdot05$). Of the 53 patients from whom adenoviruses were cultured 25 (47%) had serological evidence of infection. Conversely, of the 33 patients 'positive' by CFT, adenoviruses were isolated from 25 (76%).

In patients in whom conjunctival swabbings for isolation of adenovirus were collected during the first week of infection and in those in whom the acute samples of serum were also collected during this period and the convalescent serum within 3–5 weeks of infection (the optimum set of circumstances for each group) the cultural test was positive in 82% (41/48) and the CFT was positive in 72% (29/40). Thus, under optimum conditions the sensitivity of the 2 tests did not differ significantly.

Discussion

In this study adenovirus was isolated by the HEK cell culture system from 45% of patients with suggestive adenovirus ocular infection. This primary cell culture is shown to be as sensitive as HEp2 cells but is more sensitive than HeLa and W138 cell cultures for isolation of adenovirus (McSwiggan *et al.*, 1975).

In the present study we found that the isolation rate of adenovirus is dependent on the time of collection of specimens from the onset of ocular infection. The isolation rate obtained in specimens collected during the first week of infection was 3–5 times higher than the rate obtained in specimens collected after the first week. This finding confirms previous reports (Mitsui *et al.*, 1957, 1959; Ellison *et al.*, 1969; Dawson *et al.*, 1970) that early collection of specimens from patients with adenovirus infection is an important factor in obtaining satisfactory results from cultural tests.

In 3 patients with follicular conjunctivitis adenovirus serotypes 3 and 8 were isolated during the 8th and 9th weeks of infection. This tends to support a previous report (Darougar *et al.*, 1977) that certain adenovirus serotypes are capable of causing chronic ocular infection.

In our group of patients the CFT was a less sensitive indicator of infection than the culture test (27% and 45% of cases respectively). As with the culture test, sensitivity of the serological tests depended on the time of collection of the acute and convalescent sera. The maximum index of infection (72%) was obtained by CFT when the acute serum was collected during the first week of illness and the convalescent serum obtained not later than 5 weeks from the onset of disease. It has been shown, however, that when conjunctival swabbings for the cultural test and sera for CFT were collected at the optimum times no significant difference was observed between the sensitivity of these 2 tests for diagnosis of adenovirus infection.

The results of this study suggest that the serological responses detectable after adenovirus 7 infections are weaker than those following infection with adenovirus serotypes 3 and 8. The numbers of infections with various serotypes were too small in this study to allow a conclusion to be drawn, but this is an aspect of the serology of adenovirus ophthalmic infections which will require further study.

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An outbreak of adenovirus keratoconjunctivitis in Bristol

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SUMMARY Nineteen cases of keratoconjunctivitis caused by an adenovirus serologically related to types 10 and 19 are described. Seventeen of the patients presented over a period of 7 weeks and included 4 who were involved in a minor outbreak at a factory. The presentation and clinical features closely resembled those caused by adenoviruses types 8 and 19. Mild to severe follicular conjunctivitis, superficial punctate keratitis, discrete subepithelial opacities, membrane formation, and conjunctival scarring were all observed.

The term epidemic keratoconjunctivitis was introduced by Hogan and Crawford (1942) when they described an outbreak of this disease, noting that epidemics had been reported previously in several European countries under a variety of different names. In 1955 the causative organism was identified as an adenovirus (Jawetz *et al.*, 1955), and since that time several different adenovirus serotypes have been shown to cause conjunctivitis with and without corneal involvement (Grayston *et al.*, 1964). An outbreak in Bristol in 1971 caused by adenovirus type 8 has been described previously (Barnard *et al.*, 1973), and isolated cases and small outbreaks resulting from infections with types 10 and 19 have been diagnosed elsewhere (Heubner and Rowe, 1957; Desmyter *et al.*, 1974; Burns and Potter, 1976; O'Day *et al.*, 1976; Darougar *et al.*, 1977; Zografos, 1977).

In late September 1977 a number of patients with severe follicular conjunctivitis of probable viral aetiology presented themselves to the Bristol Eye Hospital and a member of the staff developed symptoms.

This paper describes briefly a group of patients with follicular conjunctivitis seen in the Casualty Department of the Bristol Eye Hospital between September 1977 and January 1978. It reports in detail on patients in whom the condition was shown to have been caused by an adenovirus related to both types 10 and 19, but distinguishable from the 2 prototypes.

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Materials and methods

All patients were subjected to slit-lamp examination. In patients with keratitis it was found helpful to consider the cornea in quadrants when recording the distribution of the lesions. Conjunctival swabs and blood samples were taken on presentation and on subsequent visits. Virus isolation was attempted on specimens obtained from 175 patients seen between late September 1977 and January 1978. Single or paired sera were obtained from 116 patients. Serum samples received from patients attending antenatal clinics were used to establish the approximate incidence of antibodies to adenovirus type 10/19 in the normal adult population. Bacteriological investigation was also undertaken on approximately 40% of the patients.

VIRUS ISOLATION

All swabs were sent to the laboratory in 3 ml of milk saline transport medium; 0·2 ml aliquots of this medium were routinely inoculated into cultures of Hep_2 and human embryo diploid fibroblasts (MRC 5) cells. Specimens which failed to yield a virus in these cultures were subsequently examined in cultures of human embryo kidney cells, and, if they were still negative, an aliquot of the original specimen was inoculated into organ cultures of human embryonic conjunctiva (Higgins and Scott, 1973). Isolates were identified by neutralisation tests using specific immune sera. TRIC—*Chlamydia trachomatis* was isolated in cytochalasin-treated McCoy cells (Sompolinsky and Richmond, 1974).

SEROLOGY

Paired and single sera were examined by complement fixation (CF) tests against herpes simplex virus and adenovirus antigens by overnight fixation. A haemagglutination inhibition (HAI) test using a current isolate of adenovirus 10/19 was performed on all the sera except a proportion of those from patients from whom another viral pathogen had been isolated.

Results

The commonest demonstrable cause of conjunctivitis at this time was an adenovirus serologically related to both adenovirus type 10 and type 19 (Tullo and Higgins, 1978). Of the 17 proved infections this virus was isolated from 15 of the 16 from whom swabs were obtained, the other 2 cases being diagnosed on serological grounds. A 4-fold or greater rise in CF antibody was demonstrated in 9 of 13 pairs of sera from proved cases, and an identical proportion showed a diagnostic rise in HAI antibodies. Although CF and HAI antibodies generally paralleled each other, in 2 instances a diagnosis of adenovirus infection could be made by CF but not by HAI and in 2 further cases the converse was true. Two patients with an adenovirus 10/19 infection had high (≥ 96) serum CF antibody titres and 2, a high (≥ 48) HAI titre in both sera or in a single convalescent serum sample. Only 5 of 99 sera from patients without proof of adenovirus 10/19 infection had an HAI antibody titre greater than 8, which was essentially the same proportion (7/122) as was found in serum samples obtained from patients in the asymptomatic group attending the antenatal clinics.

The observations on the epidemiology and clinical features of the outbreak of ocular infections with adenovirus 10/19 have been augmented by those made on 2 further cases seen 7 to 8 months previously. The diagnosis was based on isolation of the virus and serology in one case and serology alone in the other. The final total of 19 proved cases consisted of 11 males and 8 females with ages ranging from 19 to 59 years (average 32 years).

Other causes of conjunctivitis during this period included herpes simplex virus in 3 patients and adenoviruses types 3 and 4 in 5 and 1 patient respectively. *Chlamydia trachomatis* was isolated from 1 further patient, but all cultures for bacterial pathogens were negative. Thus a combination of isolation and serological methods enabled a diagnosis to be established for 27 of the patients with follicular conjunctivitis seen during 4 months September 1977 to January 1978.

EPIDEMIOLOGY

Thirteen of the 19 cases infected with adenovirus 10/19 could have acquired the disease from one of the other cases. It was the first patient of the outbreak who was the probable source of infection of a doctor at the Eye Hospital, who first examined him. The only other instance of presumed hospital cross-infection occurred in a 49-year-old woman who was attending the hospital as an outpatient for an anterior uveitis with secondary glaucoma in November 1976. Paired sera, taken in February 1977, when she developed disciform keratitis with central corneal oedema and folds in Descemet's membrane, showed a diagnostic rise in HAI antibodies to adenovirus 10/19. CF antibodies to herpes simplex virus were absent at a dilution of 1/8 on both occasions. This infection occurred at a time when the only other patient with a proved adenovirus 10/19 infection, who was not actually involved in the outbreak, was an inpatient at the hospital. The latter patient had been referred from another eye unit with severe keratoconjunctivitis, and a strain of adenovirus 10/19 was isolated from her conjunctiva.

An important subgroup consists of 4 patients who worked in a factory manufacturing electrical motors. The interval between the onset of symptoms in the first case and the other 3 was 7, 9, and 11 days respectively. One of this group was the factory nurse, who was exposed to infection when one of the other cases, a worker, reported to the first aid centre. This was the only instance of close contact between these patients, as, although all 4 patients knew each other, no other obvious point of contact, for example, common washing facilities, could be elicited.

SIGNS AND SYMPTOMS

The signs and symptoms of the majority of patients were typical of adenovirus keratoconjunctivitis. Patients generally complained of a painful, red, watering eye, sometimes accompanied by a foreign body sensation. Commonly symptoms were first noted on waking and increased in severity to reach a peak usually by the fourth or fifth day. The duration of these symptoms ranged from 10 days to 3 months, lasting 35 days on average. Six patients also complained of malaise and headache. Four patients complained of blurred vision, in each case related to corneal lesions, and 3 of these reported that the degree of visual disturbance varied from day to day. Visual acuity was temporarily reduced to 6/18 (corrected) in the more severely affected eye of each of 2 patients, but no patient has suffered persistent visual impairment.

Of the 19 cases 6 had signs and symptoms in 1 eye only; 4 had uniocular symptoms, but slit-lamp microscopy revealed evidence of involvement of the other eye. Nine patients had bilateral symptoms and signs, of whom only 1 was affected equally in both eyes. Examination of affected eyes indicated that the cornea and palpebral conjunctiva were characteristically involved (see Table 1).

Conjunctivitis. The papillary reactions was predominantly confined to the upper tarsal conjunctiva while follicles were recorded only in the lower fornix (Figs. 1 and 2). Scarring of the conjunctiva occurred only in those patients who had previously had an inflammatory membrane (Table 1).

Keratitis. There was corneal involvement in 13 of the 19 patients. One patient had a disciform keratitis. Eleven developed discrete stromal corneal opacities, of whom 7 had a previous or concurrent superficial punctate keratitis (Figs. 3 and 4). Four

Table 1 *Distribution and frequency of signs during the course of adenovirus 10/19 infection in 19 patients*

Site	*Sign*	*Number of patients in whom present*	*(%)*
	Follicles	18	(95)
	Papillae	18	(95)
Conjunctiva	Chemosis	5	(26)
	Inflammatory membrane	7	(37)
	Scarring	7	(37)
	Superficial punctate keratitis	8	(42)
Cornea	Subepithelial lesions	11	(58)
	Disciform keratitis	1	(5)
Regional Glands	Lymphadenopathy	7	(37)

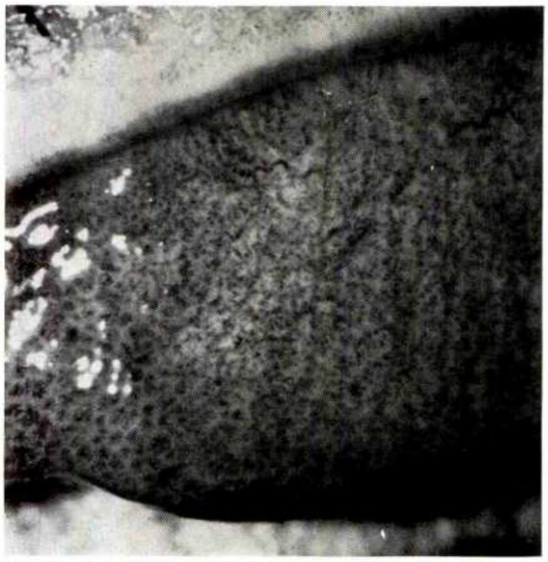

Fig. 1 *Everted upper lid showing papillary reaction*

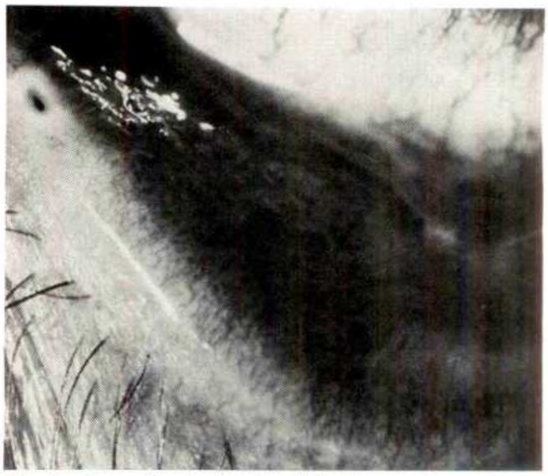

Fig. 2 *Lower fornix showing follicular reaction and conjunctival scarring*

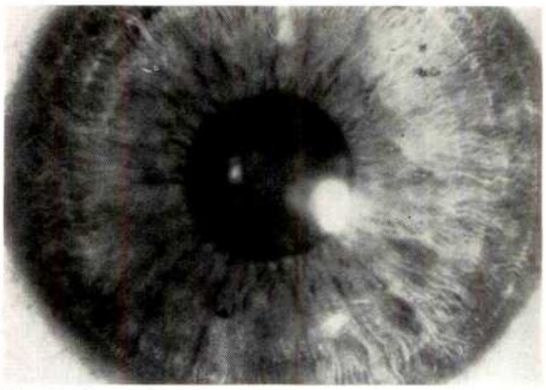

Fig. 3 *Stromal opacities seen against the pupil*

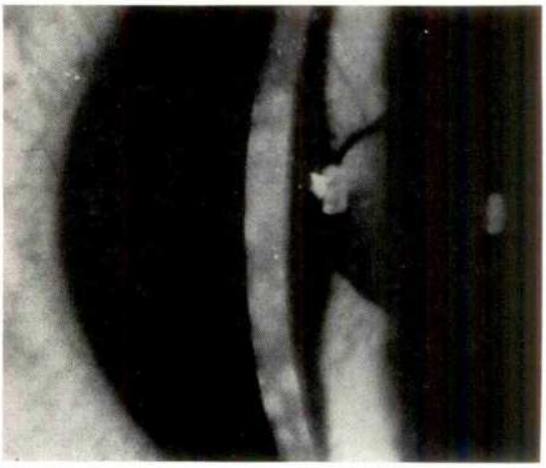

Fig. 4 *Numerous corneal subepithelial lesions seen in slit-lamp photograph*

Table 2 *The response to treatment in each eye of one patient, as measured by the number of stromal lesions and visual acuity*

		Right eye			Left eye	
Day	*Treatment (guttae)*	*Number of lesions*	*VA*	*Treatment*	*Number of lesions*	*VA*
0	Prednisone 0·25%	10	6/9	Nil	10	6/9
7	Betamethasone	10		Nil	13	
14	Betamethasone	8	6/5	Guttae betamethasone	20	6/6
21	Betamethasone	3	6/6	Guttae betamethasone	11	6/6
	Betamethasone continued for a further 20 days, then stopped. Patient reviewed after 14 days of no treatment					
55	Betamethasone	24	6/18	Nil	11	6/6
71	Betamethasone	13		Nil	6	
78	Betamethasone	7	6/6	Nil	3	6/6
	Treatment discontinued					

of these 7 were observed to have a more transient intermediate lesion which was immediately subepithelial and caused elevation of the epithelium without staining. The earliest and latest appearance of either subepithelial lesion was 10 and 35 days respectively with an average of 19 days.

TREATMENT

There is no proved treatment for adenovirus keratoconjunctivitis in the early stages, but antibiotics may be of value in palliating symptoms and preventing secondary infection (Dudgeon *et al.*, 1969; Dawson *et al.*, 1970). All patients in this outbreak received topical chloramphenicol initially. One patient had additional treatment with acetyl cysteine 10%, with dispersion of a developing inflammatory membrane but failure to prevent conjunctival scarring.

Prednisolone drops (Predsol) 0·25%, 4 times a day, were given to all patients who developed subepithelial lesions. With an uncomplicated response and persisting lesions the dose of steroids was increased by giving betamethasone (Betnesol) drops 4 times a day. Partial or complete resolution of the corneal lesions was noted in all patients thus treated.

Three patients merit further mention of their response to treatment. One, the brother of a patient seen during the acute stage, presented 6 weeks after the onset of symptoms because he had developed blurring of vision. Examination of the affected eye revealed a 'snow-storm'-like cornea with profuse stromal lesions (approximately 120). He was treated with betamethasone drops for 16 days and his vision improved from 6/9 to 6/5, by which time the lesions were scarcely discernible. He has suffered no further episodes of blurred vision.

The second patient was equally affected in both eyes, and 38 days after onset of symptoms he was left with 10 subepithelial opacities in each. Initially steroid therapy was restricted to 1 eye, the untreated eye serving as a control, but when the treated eye improved and the untreated deteriorated steroids were instilled into both eyes (Table 2).

A third patient, first seen in January 1977, had developed subepithelial opacities by 3 weeks after the onset of symptoms and the visual acuity had fallen to 6/18 in each eye. With steroid therapy she improved, and when she was followed up 9 months later 8 stromal opacities were noted to have persisted in the central cornea of the right eye. The visual acuity was 6/9 and 6/5 in the right eye and left eye respectively. At this time she was experiencing intermittent blurring of vision in the right eye. She was last seen 18 months after the initial infection and still complained of blurring of vision which gave rise to difficulties with her clerical job. Examination revealed a white eye with approximately 30 faint large opacities immediately subepithelially, mostly in the upper marginal cornea of the right eye. She had a Hudson-Stahli line in the right eye and a small central area of pigmentation in the left, neither of which was previously present.

Discussion

The epidemiological and clinical features of these adenovirus 10/19 infections were very similar to those found in 'classical' adenovirus keratoconjunctivitis caused by type 8 and more recently by type 19 (O'Day *et al.*, 1976). Spread of the 10/19 virus within the community was uncommon, with only 5% of the adults having antibodies, a similar proportion to that found previously in Bristol for type 8 adenovirus (Barnard *et al.*, 1973). This might be expected, as adenoviruses types 8, 10, and 19 all belong to the same subdivision, group II, 1 of 4 groups into which adenoviruses are divided on their haemagglutination properties (Rosen, 1960). The term 'epidemic keratoconjunctivitis' perhaps now justifies the inclusion of these serotypes rather than specifically referring to infections caused by serotype 8. Of other adenoviruses commonly associated with conjunctivitis types 3 and 7 belong to group I and type 4 to group III. None the less, the variation in severity of the symptoms and the lack of pathognomonic signs makes the accurate diagnosis of adenovirus follicular conjunctivitis difficult. Eleven such cases in this study were shown to be infections with agents other than the adenovirus type 10/19. The close correlation between the results of virus isolation and serology suggests that very few, if any, of the cases in which a diagnosis was not established were in fact infections with adenovirus 10/19.

The ease with which conjunctivitis caused by adenovirus type 8 can be spread, especially by medical personnel, is notorious (Thygeson, 1957; Dawson *et al.*, 1972). The relatively few secondary cases in this outbreak would indicate that the organism was of low virulence or, more probably, that preventive measures recommended previously (Clarke *et al.*, 1972), such as hand washing between examining patients, were effective.

While the constituent features of patients with this infection were typical of group II keratoconjunctivitis, the incidence and degree of chemosis was notably less than that sometimes seen in outbreaks caused by other serotypes (Hart *et al.*, 1972). The proportion of patients who developed conjunctival scarring was high (Table 1).

In this study the average interval from the onset of symptoms to the appearance of subepithelial opacities was 1 to 2 weeks. However, the interval to opacity-related symptoms may be considerably longer, as shown by the patient who presented for the first time 6 weeks after the initial infection complaining of blurred vision. Subepithelial opacities were always more pronounced in the eye in which symptoms developed first, and these lesions are liable to become more pronounced and numerous after the abrupt stoppage of steroids (Table 2). The incidence of subepithelial lesions (58%) was lower than that described in infections caused by adenovirus type 8 (82%) (Barnard *et al.*, 1973).

It is thought that punctate subepithelial lesions result from the interaction of viral antigen and antibody in the anterior stroma, the cornea acting as a blotter (Jones, 1958). At the time of infection the virus becomes established in the epithelium, producing a superficial punctate keratitis. Infective virus is seldom demonstrable after 10 to 14 days, but this does not exclude the continued production of viral antigens (Pereira, 1972). That the epithelium is important in facilitating this antigenic stimulus is suggested by the fact that in patients with epithelial erosions the disease rarely progresses to the stage of typical subepithelial infiltrates (Laibson, 1975).

The patient who developed a disciform keratitis is of considerable interest. She was the only patient to have neither follicles nor papillae. Not only are these unusual features of adenovirus infection, but she was the only patient to have had previous ocular disease. Although anterior uveitis occurs in adenovirus disease, the diagnostic rise in CF antibody titre to adenoviruses from $<1/8$ during the development of the disciform keratitis suggests that the preceding uveitis had a different cause. Other investigations were negative. In the disciform keratitis of herpes simplex virus there is evidence of delayed hypersensitivity (Swyers *et al.*, 1967). However, it is not clear how the mechanisms producing discrete punctate stromal lesions and disciform keratitis differ; indeed, both may occur together (Hogan and Crawford, 1942). On clinical grounds this patient was treated as a case of herpetic keratitis and given topical idoxuridine and low-dosage steroids. The diagnosis was made in retrospect on a rise in HAI antibodies. Gradual resolution took place over a period of 8 months, and she was left with a Hudson-Stahli line in the affected eye, but the cornea was otherwise normal. She was thus the second patient observed to develop such pigmentation during the late follow-up.

The response observed to the application of topical steroids substantiates previous reports of their usefulness in resolving subepithelial lesions (Dawson *et al.*, 1972). As it is rare for stromal opacities to occur without preceding superficial punctate keratitis, it is possible that many stromal lesions are preventable, although the use of prophylactic steroids with its attendant risks is debatable (Laibson *et al.*, 1970), and withdrawal of steroids may precipitate a recurrence of stromal opacities (Table 2).

Further investigations are proceeding to establish the precise relationship between the adenovirus involved in this outbreak and the type 10 and 19 prototype viruses. Meanwhile, it is interesting to note that an adenovirus showing similar antigenic cross-reactions has been isolated in Holland in association with small outbreaks of keratoconjunctivitis resembling the one reported here (de Jong *et al.*, 1978). An awareness that such variants are circulating will serve to prevent confusion in the typing of strains isolated from future outbreaks of epidemic keratoconjunctivitis.

We are grateful to the staff of the Eye Hospital Casualty Department for the collection of specimens, to Mr J. Morgan for photographs, and to Mr D. Easty and Mr J. C. Dean Hart for encouragement and advice. We are also indebted to Dr S. K. R. Clarke and the staff of the Public Health

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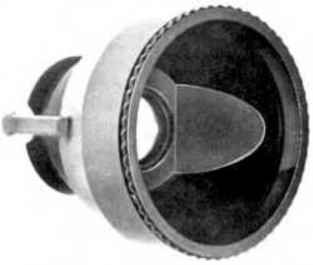
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Phlyctenular eye disease in association with *Hymenolepis nana* in Egypt

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SUMMARY It had been previously noticed that infection with parasites was common in children suffering from phlyctenulosis. In the present study the stools of 471 patients suffering from phlyctenular disease were examined and it was found that 62·6% of them had *Hymenolepis nana* ova in their stools as compared with 10·8% of the controls. All patients had *Hymenolepis nana* immune sera. Many of these patients had abdominal symptoms. *Hymenolepis nana* is a cestode parasite discovered by Bilharz in Cairo in 1851. Infections with it have the same age incidence and geographical distribution as phlyctenular eye disease. It has a tissue stage responsible for a state of hypersensitivity which is thought to be responsible for the phlyctenules.

Phlyctenular keratoconjunctivitis is a disease occurring mainly in children, with a slight preponderance of males. In Egypt it is very common, constituting about 20% of cases of acute conjunctivitis (Al-Hussaini and Saoudi, 1968). It is known to be an allergic response of the corneal and conjunctival epithelium to an endogenous toxin. The most accepted theory was that this toxin is a tuberculoprotein. In 1968 Al-Hussaini and Saoudi found that tuberculoprotein does not seem to be a factor in phlyctenular eye disease in Egypt. Bakly (1929) attributed a high incidence of phlyctenular eye disease in Port-Said, Egypt, to ascariasis. Jeffery (1955) found that *Ascaris lumbricoides, Ancylostoma duodenale, Enterobius vermicularis,* and *Entamoeba histolytica* are responsible for a number of eye diseases, phlyctenulosis being the most common.

Al-Hussaini *et al.* (1977) found that phlyctenular eye disease in Egypt is often associated with intestinal infection with *Hymenolepis nana* (the dwarf tape worm). A careful examination of the stools of 155 cases of phlyctenular eye disease showed that 57·4% of them had *H. nana* ova in their stools. In cases of multiple or recurrent phlyctens the eggs were found in 73·4% of cases.

That preliminary study, pointing to *H. nana* having an important role in the aetiology of phlyctenular eye disease, suggested the need for more evidence. The stools of a larger number of cases were therefore examined, the serum was tested for antibodies, and a specific anthelminthic drug was given to some patients.

Material and methods

This study includes 471 cases of phlyctenular eye disease, while 157 cases in the same age groups were used as controls. The age and sex, the social condition, and the presence of any abdominal symptoms were noted. The stools of both groups were examined by both the direct and the more sensitive flotation methods (Faust *et al.*, 1975).

In addition to the examination of stools of another 64 cases of phlycten their sera were tested for any circulating antibodies. The sera of 16 controls were also tested. About 2 ml of blood were taken into a closed sterile test-tube. This was left in the slanting position until serum was separated. With sterile Pasteur pipettes serum was pipetted into sterile small vials, which were preserved at −4°C until being used.

Living *H. nana* worms were obtained from the small intestines of laboratory white rats or mice. The test was done after leaving the sera to warm at room temperature. Serum of every case was added separately to few segments of the living strobila of the worm. Immune sera affect adult worms by

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Table 1 *Incidence of different parasites in phlycten cases and controls*

	Total number of cases of phlyctenular disease (471)				*Controls (157)*			
	Male	*Female*	*Total*	*%*	*Male*	*Female*	*Total*	*%*
Hymenolepis nana	179	116	295	62·63	10	7	17	10·82
Ancylostoma duodenale	14	4	18	3·8	3	0	3	1·91
Enterobius vermicularis	8	17	25	5·8	2	1	3	1·91
Strongyloides stercoralis	0	0	0	0·0	0	0	0	0·0
Ascaris lumbricoides	0	1	1	0·21	0	0	0	0·0
Trichostrongylus colubriformis	0	1	1	0·21	0	0	0	0·0
Giardia lamblia	2	1	3	0·63	1	0	1	0·63

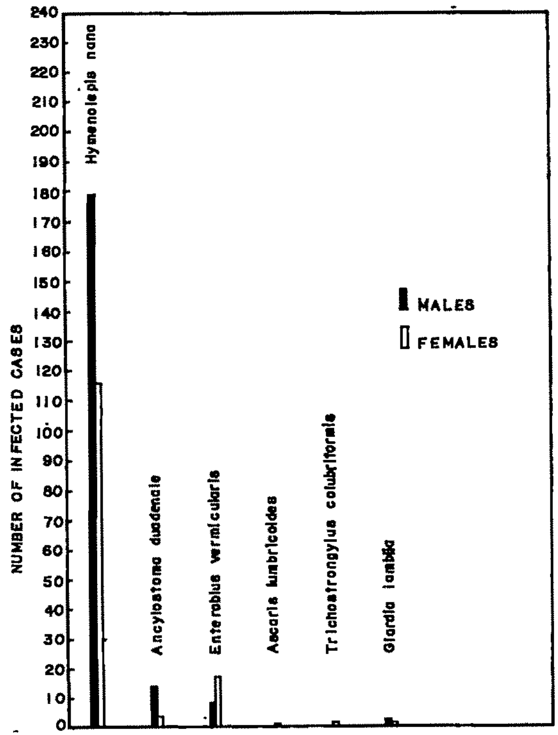

Fig. 1 *Incidence of different parasites in phlycten cases*

completely enveloping them in a layer of precipitate and rupturing the cuticle (Heyneman and Welsh, 1959).

Two phlyctenular cases who were found to be strongly infected with *H. nana* were admitted to hospital. They were given Niclosamide (Yomesan), which is the anthelmintic drug specific for *H. nana*, without the use of steroids or any other topical application to the eyes. In the period of study only these 2 patients accepted admission to hospital; treatment as outpatients is unreliable.

Results

Table 1 and Fig. 1 show the result of stool examination of 471 patients suffering from phlyctenular eye disease and 157 controls. Out of 471 cases 295 had *H. nana* ova in their stools, or 62·63%, as compared with 17 out of 157 controls, or 10·82%. There was no significant difference between the incidence of other parasites in phlyctenular eye cases and controls (Figs. 1 and 2). Of 295 cases of phlycten 260 had

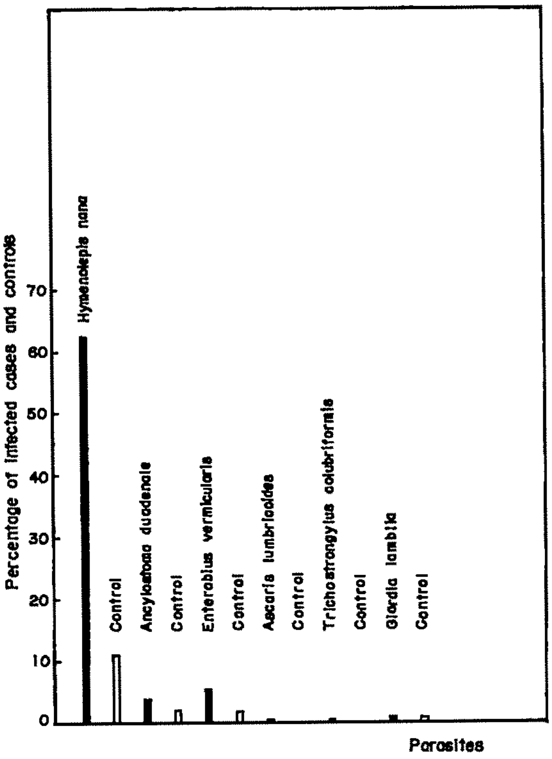

Fig. 2 *Percentage of infection with different parasites in phlycten cases and controls*

Table 2 *Incidence of* Hymenolepis nana *ova in cases with multiple phlyctens*

	+*ve* H. nana	− *ve* H. nana	*Percentage*
Multiple phlycten (84)	63	21	75

Table 3 *Age incidence of cases of phlycten*

Age (years)	*Number of cases*	*Percentage*
1–10	266	56·48
11–20	149	31·63
Over 20	56	11·89
Total	471	

Table 4 *Age incidence of cases of* Hymenolepis nana

Age (years)	*Number of cases*	*Percentage*
1–10	189	60·58
11–20	96	30·77
Over 20	27	8·65
Total	312	

H. nana ova only in their stools; the remaining 35 had mixed infection mostly with *Ancylostoma duodenale* and *Enterobius vermicularis.*

Multiple infection with phlyctenules was found in 84 cases; 63 of them had *H. nana* ova in their stools, or 75% (Table 2).

The age incidence of patients with phlyctenular eye disease is shown in Table 3, and that of patients with *H. nana* eggs in their stools in Table 4 and Fig. 3.

Both stool and serum examinations were done on 64 phlyctenular cases. The ova of *H. nana* were found in the stools of only 38 of these patients, while a serum test for circulating antibodies showed that all the patients had *H. nana* immune sera. Within a few minutes an enveloping layer was formed round the living segments, which sooner or later ruptured. Although the test was not done quantitatively, it was noticed that the reaction was more powerful and occurred more rapidly in cases of mutliple phlyctenules. As a control the sera and stools of 16 phlycten-free cases were tested in a similar manner. Although one control case was harbouring ova of *H. nana* in the stools, the serum of all the 16 controls failed to give any reaction round the living segments of worms (Table 5).

The 2 inpatients who were given niclosamide (Yomesan) for treatment of *H. nana* were cured of the symptoms of phlyctenular keratoconjunctivitis within a few days without the use of any other systemic or topical remedies.

Many patients gave a history of vague abdominal symptoms in the form of diarrhoea and colic.

Discussion

Hymenolepis nana was discovered by Bilharz in 1851 in the small intestine of a native boy at necropsy in Cairo, Egypt. It affects 10% of children in Egypt and Sudan (Belding, 1952). 62·63% of patients with phlyctenular eye disease had *H. nana* ova in their stools. This incidence rises to 75% among patients with multiple phlyctens. The eggs of other parasites were significantly fewer than those of *H. nana*. The ova of *H. nana* are not easily detected microscopically. Hence the most careful search should be done

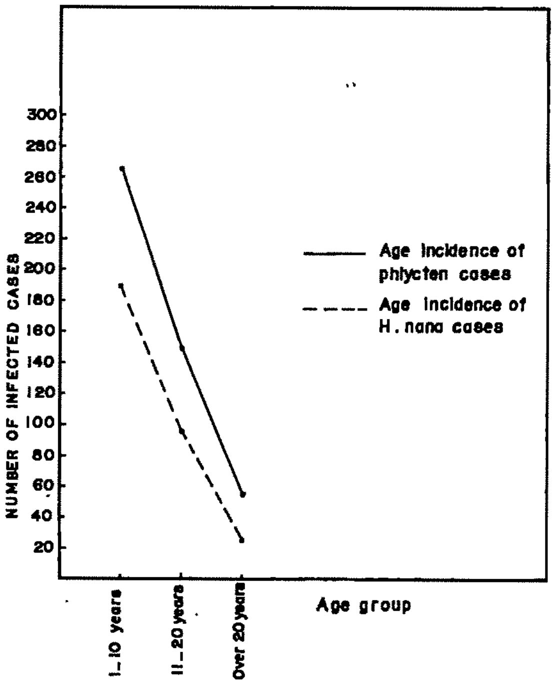

Fig. 3 *Age incidence of phlycten cases and* H. nana *cases*

Table 5 *Results of serum and stools examination of phlycten and control cases*

	Number of cases	*Positive stools*	*%*	*Positive serum*	*%*
Phlycten	64	38	53·1	64	100
Control	16	1	6·2	0	0

by a trained observer by both the direct and flotation methods.

The life cycle of *H. nana* in the human body was described in our preliminary report (Al-Hussaini *et al.*, 1977). Most important in this respect is the presence of a tissue stage of the parasite. The larval stages (cysticercoids) penetrate into the villi of the small intestine, where they complete their maturation for about 7 days before they return into the lumen of the intestine. As the parasite is not restricted to the gut, the degree to which it comes into contact with tissue fluids and serum of the host is increased. The development of helminths from the embryonic and larval stages to the sexually mature forms must include biochemical and physiological changes, all of which make the antigenic mosaic increasingly complex (Sinclair, 1970). Several workers have shown that different stages of the worms can elicit different types of antibodies in the host which are to some degree stage-specific, but it is also known that, at least for some helminths, 1 stage is as efficient as another in stimulating immune bodies.

Sinclair (1970) stated that little is known about enzymes which might help the parasite in its invasion of the host tissue, and consequently even less is known about the antibodies which these might stimulate. However, Bogitsh (1967) demonstrated esterases and an alkaline phosphatase in *H. nana* cysticercoids. As more is learnt about the type and location of these enzymes in the parasite and the sequence in which they are found in the life cycle, their effect on the immunological status of the host will become better understood.

Although little success has been obtained in vaccinating animals with dead helminthic material, Coleman *et al.* (1968) found that *H. nana* homogenate when injected into mice confers a strong immunity. This is further evidence that *H. nana* is an antigenically strong parasite.

The absence of ova in the stools of some patients with phlyctenular eye disease can be explained by intermittent passage of eggs and by the fact that an allergic response to helminths may persist for a long time after disappearance of the parasite from the body. Moreover, helminths may enhance allergic reactions to unrelated antigens (Ershov *et al.*, 1974). The determining factor for the development of phlyctens is not the presence of ova in the stools but the state of hypersensitivity induced by the cysticercoid stage of the parasites. On the same grounds we can explain why some controls have had eggs of *H. nana* in their stools although they did not complain of eye phlyctenules.

The eggs of *Ascaris* were found in only 1 case during the present study. Bearing in mind that the eggs of *Ascaris* are easily seen in the stools because of their great number and their conspicuous appearance and knowing that *Ascaris* is a parasite that has no tissue stage, we consider that *Ascaris* plays no role in phlyctenular eye disease.

Ancylostoma was found in 3·8% of cases and in 1·91% of the controls. The general incidence is low, and the difference between the cases and controls is insignificant. Moreover, *Ancylostoma* was often associated with *H. nana* in the same patient.

Enterobius vermicularis is best diagnosed by a perianal swab and not by stool examination. In view of the fact that it is a very widely spread parasite among Egyptian children as compared with the incidence of phlyctens among them, and that it is an intestinal parasite that has no tissue stage, it is very unlikely to be responsible for the development of phlyctens.

Amoebiasis is excluded as a factor because it is not associated with eosinophilia or any allergic manifestation (Chandler, 1970).

Abdominal complaints were common among children with phlyctenular eye disease, though accurate statistical data of symptoms definitely related to *H. nana* were impossible because of the prevalence of bowel disturbances of various origins among Egyptian children.

Conclusions

All cases of phlyctenular eye disease had *H. nana* immune sera. Most of them have *H. nana* ova in their stools. Phlyctenules and infection with *H. nana* have the same age incidence and geographical distribution. Abdominal symptoms are common in patients with phlyctens. Two cases of phlycten eye disease responded dramatically to specific anthelmintic treatment. Other parasites are excluded. It is therefore obvious that the state of hypersensitivity caused by the cysticercoid stage of *H. nana* is responsible for the development of phlyctenules in Egypt.

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Surgical management and histopathology of invasive tumours of the cornea

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SUMMARY Four cases of conjunctival squamous carcinoma invading the cornea are presented. The surgical technique of excising the tumours from the cornea by lamellar keratectomy is described. Histology of the lesions showed well differentiated squamous carcinoma invading the superficial layers of the cornea only. Large invasive squamous cell carcinomas of the cornea result because of neglect of small paralimbal tumours and can be adequately removed by lamellar keratectomy, leaving the globe intact.

The commonest tumours that involve the cornea are carcinomas arising at the limbus. Large tumours that invade the cornea tend to be well differentiated squamous cell carcinomas. These tumours grow as an exophytic mass, probably because of the protective thickness of the corneal tissue. Zimmerman (1965) has stated that he has seen a number of cases in which the eye had been enucleated because the limbal tumour seemed to have involved so much of the cornea or because it had grown so large. Zimmerman believes that the eye might well have been saved by a courageous surgeon, because often in the case of the spreading 'in situ' cancers that involve much of the corneal surface the opacification, vascularisation, and pannus formation that are so impressive clinically are found histologically to be very superficial. Zimmerman believes that an extensive superficial keratectomy would have sufficed in a number of cases that were treated by enucleation.

We wish to present our experience in treating 4 patients with invasive carcinomas of their corneas.

Patients and methods

Four Bantu-speaking South African Negroes were seen at the St. John Eye Hospital, Baragwanath. Each of the patients presented with a large limbal mass extending well on to and being fixed to the adjacent cornea.

The first patient was a male aged 62 years. He presented with a conjunctival mass in his right eye which had invaded almost the total corneal surface. Visual acuity was perception of light, and no anterior chamber structures could be seen (Fig. 1). The second patient was a 67-year-old female. In her right eye a limbal conjunctival mass had invaded the lower third of the cornea, the upper half of the cornea being clear of the mass (Fig. 2). The third patient, a male aged 60 years, presented with a large

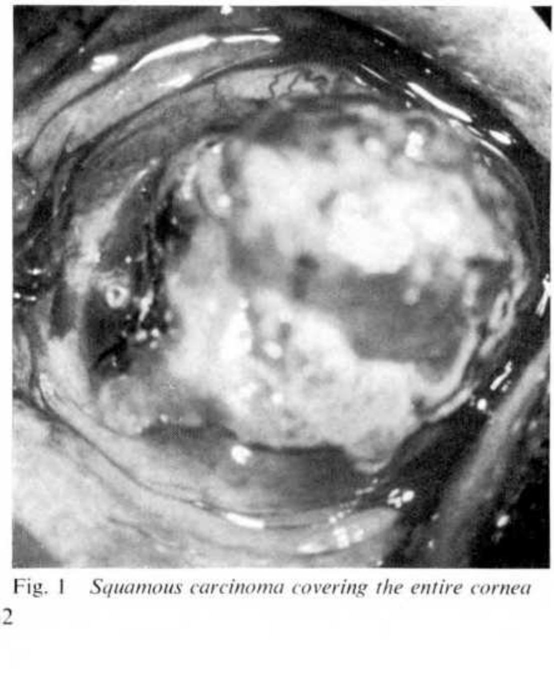

Fig. 1 *Squamous carcinoma covering the entire cornea*

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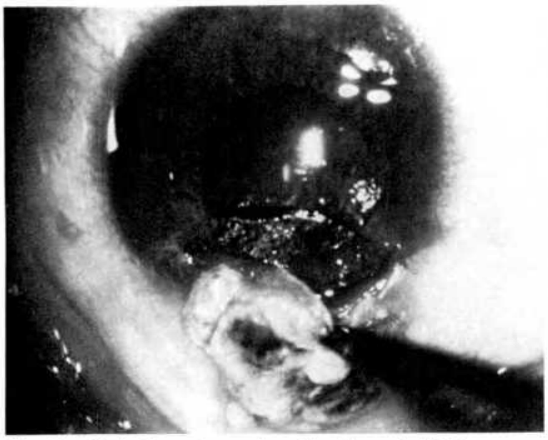

Fig. 2 *Limbal carcinoma invading lower half of cornea*

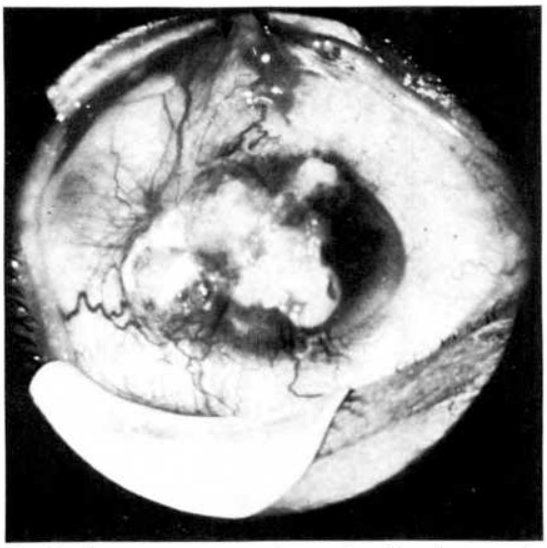

Fig. 3 *Large squamous carcinoma invading almost entire cornea*

conjunctival tumour extending from the limbus on the nasal side to almost cover the entire cornea (Fig. 3). The final patient was a 50-year-old male presenting with a limbal mass which had invaded the right cornea from the nasal side.

All the above patients underwent lamellar keratectomy to remove the invading mass. An incision was made in clear cornea just beyond the furthest area of tumour invasion; it was made into the upper third of the corneal stroma. A plane between stromal lamellar found in the upper third of the cornea and the dissection was continued beneath the invading tumour until the limbus, from where the tumour was arising, was reached. At the limbus the dissection became superficial once again, and a wide excision of conjunctiva containing the tumour mass was carried out. The sclera adjacent to the involved limbal area was left bare of conjunctiva, and bleeding was stopped by cauterisation. When the tumour was very large almost the entire perilimbal area was left free of conjunctiva (Fig. 4). All the excised tumours were sent for histological examination.

Results

The 4 corneas had similar carcinomas of their epithelial surfaces. The carcinomas as shown in the photomicrographs are of a well-differentiated superficial squamous type. Invasion is into the outer lamellae of the stroma only, and a moderate non-specific round-cell infiltrate is present beneath the carcinomas in the deeper stromal layers. In all the sections the lamellar keratectomy is seen to remove the carcinomas adequately both circumferentially and in depth (Fig. 5).

Discussion

Squamous cell carcinomas of the conjunctiva usually arise at the limbus and spread to the cornea and adjacent bulbar conjunctiva. The limbal carcinoma may invade the sclera and much more rarely the cornea (Ash, 1950). As carcinomas tend to arise at sites of epithelial transition it is consistent for the limbus to be the place of predilection. Most limbal carcinomas are removed when they are relatively small and have not invaded cornea. It is rare to see large invasive tumours of the cornea as presented in the above 4 cases, and this occurs only

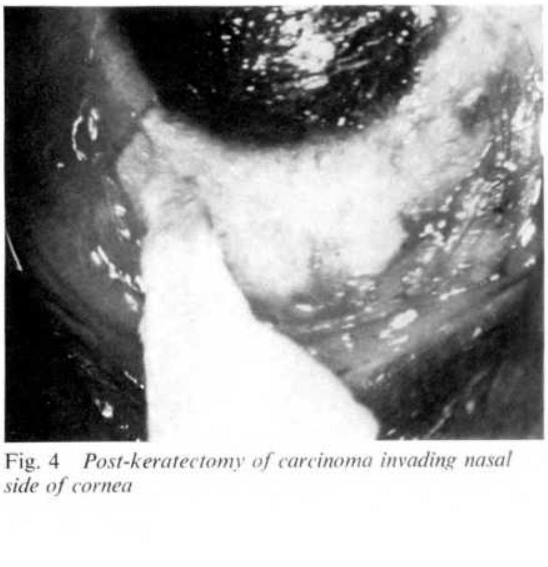

Fig. 4 *Post-keratectomy of carcinoma invading nasal side of cornea*

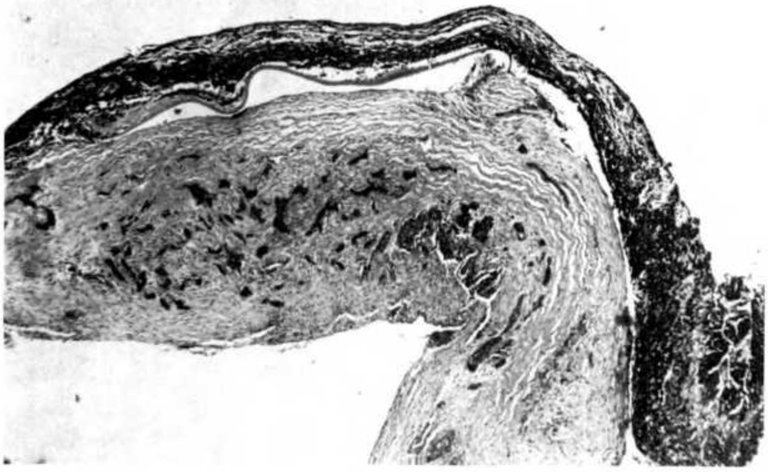

Fig. 5 *Irregular, thick, and keratinising corneal epithelium, covers inflamed neovascularised stroma. The epithelium is malignant, and microinvasion into stroma is present. Lamellar keratectomy has removed carcinoma completely (× 800)*

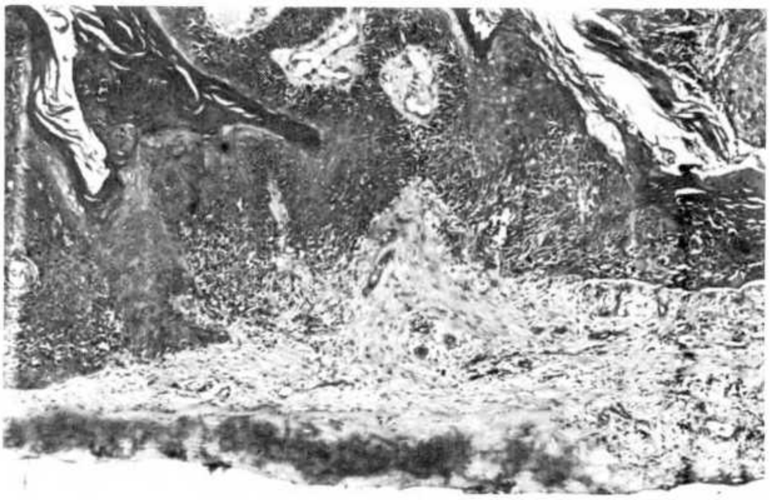

Fig. 6 *Islands of invading squamous carcinoma are present in the corneal stroma, and invasion into adherent iris is present (× 800)*

as a result of neglecting the lesion when it is small and localised. The 4 cases described illustrate the well-known pathological feature of squamous carcinomas of the conjunctiva, characterised by superficial invasion of adjacent structures even if the tumour is of a large size.

Bowman's membrane offers considerable resistance to the deep invasion of the tumour, and even tumours involving the entire corneal surface may not have penetrated into stroma. This feature is important from a therapeutic aspect, as even very large tumours invading large areas of cornea may be adequately removed by superficial keratectomy, as is indicated in the 4 cases presented by us.

Ash and Wilder (1942), in discussing limbal tumours came to the conclusion that local excision will suffice in the majority of cases and that enucleation is necessary only if recurrences are persistent. They also claimed that limbal tumours tended to invade the cornea rather than extend peripherally, and this has been our experience as well. Extension of a limbal carcinoma into the eye is an extremely rare occurrence.

We have seen 1 patient who had a phthisical eye removed and was found to have a squamous carcinoma which had penetrated the eye (Fig. 6). As the patient gave a previous history of trauma, the tumour may well have penetrated through a perforating injury.

Squamous carcinoma of the conjunctiva tends to spread to cornea rather than peripherally. The cornea is resistant to deep spread of the tumour, which may be adequately excised by lamellar keratectomy irrespective of the size or extent of spread on to the cornea. Enucleation would appear to be rarely necessary in the management of invasive carcinomas of the cornea.

We thank the Medical Superintendent of the Baragwanath Hospital for permission to publish these case reports, and Dr L. Joffe for referring Cases 1 and 3 to us.

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Trabeculectomy in Nigerian patients with open-angle glaucoma

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SUMMARY Filtering procedures for glaucoma in Africans are considered to be failures owing to their propensity for increased fibrosis. However, favourable results from trabeculectomy in African patients with glaucoma are reported. Most of these are from such modifications of technique as non-suturing of flaps, sclerectomy, posterior lip cautery, or administration of high doses of steroids. In this study 95·4% success with a virtual absence of complications is reported from a standard technique of trabeculectomy and no steroids.

Visual deficit and blindness resulting from glaucoma in Nigeria are considerable. Open-angle glaucoma is the commonest type encountered. Angle-closure glaucoma and acute congestive episodes are rare. Surgery for glaucoma forms 18% of all intraocular surgery at the Ophthalmic Unit of Ahmadu Bello University Teaching Hospital. This is because surgery is the only satisfactory method of treating the great majority of glaucoma patients here (Keitzman, 1976; Sandford-Smith, 1978).

Traditionally filtration procedures are considered to be ineffective in Africans wherever they may be, owing to a racial propensity to excessive scar formation (Welsh, 1970). So cyclodiathermy and cyclodialysis were preferred as the first procedures for African patients (Stocker, 1945; Becker, 1958). Because of the deep-rooted concept of filtration failure a trabeculectomy procedure has been modified to improve results in the African by such means as excising Tenon's capsule, non-suturing, loose suturing, or minimal suturing of the scleral flap (Welsh, 1972; Freedman *et al.*, 1976; Keitzman, 1976; Fergusson and MacDonald, 1977; Sandford-Smith, 1978), sclerectomy, iris inclusion (Welsh, 1972), cauterising the posterior lip and beyond (Schimek and Williamson, 1977). or adding a regimen of high doses of corticosteroids (Fergusson and MacDonald, 1977). Favourable results, however, have been reported from trabeculectomy without such measures (Chatterjee and Ansari, 1972; David *et al.*, 1977).

In this paper we present high rates of success and virtual absence of complications from trabeculectomy without recourse to additional techniques or medical management in a wholly African group of patients with open-angle glaucoma in Nigeria. We describe certain aspects of the surgical techniques conducive to such favourable results.

Material and methods

Trabeculectomy was done in 139 eyes (104 bilaterally, 35 unilaterally) of 87 patients with open-angle glaucoma aged between 36 and 72 years. 111 eyes (44 males, 18 females) were followed up for a minimum period of 6 months and a maximum of 19 months. Their visual status ranged from perception of light (PL) or counting fingers (CF) to 6/6 to 6/5. Their intraocular pressures (IOP) ranged between 30 and 70 mmHg. The cup/disc ratio ranged from 0·6 to endstage cupping. Their fields corresponded largely with the disc changes. All patients were Nigerians and all were seen and operated on by the authors under general anaesthesia (except 4 which were done under sedation and local anaesthesia by registrars under close supervision by the authors) at the Guinness Ophthalmic Unit of Ahmadu Bello University Teaching Hospital, Kaduna, Nigeria.

Each patient was admitted the day before operation after diabetes, hypertension, or other systemic conditions had been brought under control by a physician. Antiglaucoma medication (pilocarpine 2% and/or epinephrine borate (Epinal 1%) and/or acetazolamide (Diamox) was prescribed as indicated as soon as the diagnosis was made in the outpatient

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Table 1 *Patients and eyes*

	Patients				*Age*		*Eyes*		
	Total	*Percentage*	*Male*	*Female*	*Minimum*	*Maximum*	*Total*	*Bilateral eyes/ Patients*	*Unilateral eyes*
Operated	87						139	104/52	35
Followed-up	62	71·3	44	18	36	72	111	98/49	13

Table 2 *Follow-up*

Duration	*Patients*	*Percentage*
6 to 11 months	33	53·23
12 to 19 months	29	46·77

Table 3 *Visual status of follow-up patients*

	Both eyes	*One or both eyes*	*One or both eyes*
	PL/CF to 6/60	*6/36 to 6/18*	*6/12 to 6/5*
Patients	17	24	21
Percentage	27·42	38·71	33·87

department and was continued until and including the day of admission. The average duration of this period of medical management was 1 month.

No antiglaucoma medication was given on the day of operation, nor postoperatively unless there was any complication. No systemic corticosteroids were given before or after surgery. No subconjunctival depot steroid was given at surgery. Pilocarpine 2% drops were instilled immediately after iridectomy, followed by atropine 1% drops at the end of the operation. Steroid and atropine drops were regularly used from the first postoperative day, and continued for about 6 weeks or until all signs of inflammation subsided. If both eyes were affected, both sides were operated on at the same time. In all cases the excised piece of sclerocornea was examined histopathologically. Postoperatively there was no restriction of movements once the patient was out of anaesthesia. A daily inspection and dressing was routine.

A tonometry was done on the day of discharge (5th or 6th day) and on every visit (every week for 3 weeks, at the 6th week, monthly, and then every 3 months for 1 year, 6-monthly in the following year). Gonioscopy and functional status were reviewed at these visits.

TECHNIQUE

General anaesthesia (halothane, nitrous oxide, oxygen) was given in all cases except for 4 eyes done under local anaesthesia with sedation. A 2·5-times operating loupe was used for magnification, though an operating microscope was used to confirm landmarks and for teaching.

Generally Watson's (1972) modification of the trabeculectomy of Cairns (1969) as described by Galin *et al.* (1975) was used except as follows.

(*a*) *Conjunctivo-Tenon's flap.*—Tenon's layer was not excised. Two types of flaps were fashioned: (*i*) classical, large, limbal based, turned over the cornea (68 eyes); and (*ii*) semi-fornix-based triangular flap (43 eyes) (Figs. 1 and 2). The conjunctiva is incised and undermined at the limbus from 10.30 to 2 o'clock or less and cut posteriorly for 8 to 10 mm on one side, the position depending on a superomedial or superolateral trabeculectomy. The triangular flap is reflected away from the site of operation, giving excellent exposure. At the end of surgery this flap is drawn taut to hug the limbus firmly and anchored, the first suture taking a deep bite at the anterior end of the posterior directed incision; 1 or 2 additional sutures may be applied at the limbus or a continuous one. The excess of the flap may be excised and the incision closed by interrupted or continuous sutures, or brought down to be sutured to the original incision.

(*b*) *Scleral site.* An area superolateral or superomedial or central, devoid of large vessels, is chosen. This area is lightly heat-cauterised. No cautery is applied after the scleral incision is made.

(*c*) *Size and thickness of superficial scleral flap.* The size varied between 4·5 and 5·5 mm at the limbus and 4·5 and 5 mm posteriorly, depending on the site chosen; large vessels were avoided, particularly the perforating anterior ciliaries. The thickness was always more than two-thirds, leaving a thin bluish posterior layer. Anteriorly dissection extended about 1 mm into clear cornea to include all trabecular tissue.

(*d*) *Inner flap.* This was as thin as possible and always 3×3 mm, so that about 1 mm was left for perfect closure and to prevent inadvertent cyclodialysis. The direction of dissection was from posterior to anterior after mapping out the course. A blade fragment was used, the sharp edge for cutting and the blunt edge for detaching ciliary body from scleral spur. In this way any cyclodialysis was avoided except for the excised area. The flap was excised at the anterior level of the superficial flap by the blade and sent for histopathological study.

(*e*) *Iridectomy*. The iris was abscissed in the horizontal axis with a medial and lateral pull, so that a widely based peripheral iridectomy resulted. Pilocarpine 2% drops were instilled immediately after iridectomy. No iris repositor was used.

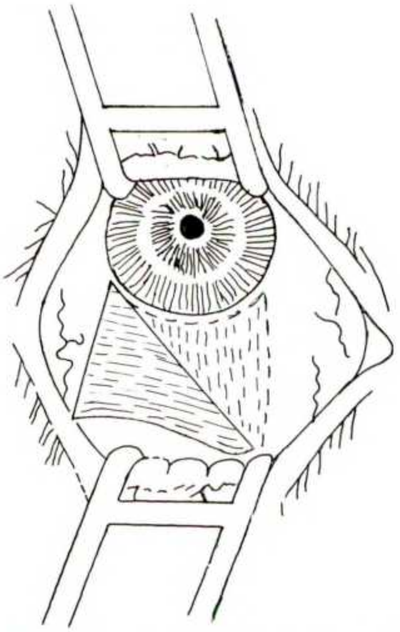

Fig. 1 *Triangular conjunctiva-Tenon's flap reflected*

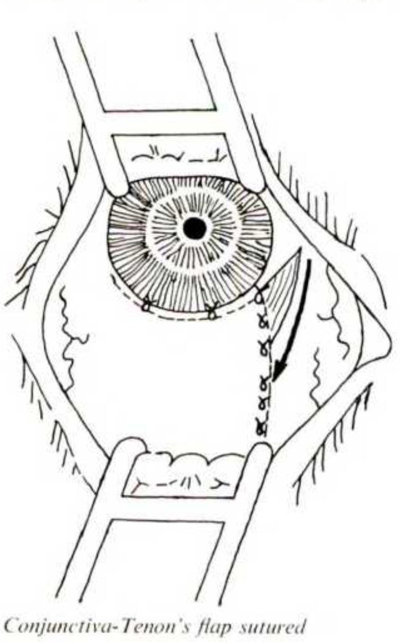

Fig. 2 *Conjunctiva-Tenon's flap sutured*

Table 4 *Control of intraocular pressure*

IOP applanation	*Eyes*	*Percentage*
20 mmHg or less	106	95·4
Above 20 mmHg	5	4·6

Table 5 *Postoperative intraocular pressure in 111 eyes*

IOP applanation	*Eyes*	*Percentage*
35 to 21 mmHg	5	4·6
20 to 14 mmHg	85	76·5
13 to 8 mmHg	17	15·3
Below 8 mmHg	4	3·6

(*f*) *Suturing*. Seven to 12 sutures are applied, the number depending on the size of the superficial scleral flap. A fine absorbable suture was used (7/0, 8/0 Vicryl or 8/0 virgin silk when Vicryl was not available). The anterior 2 sutures at the corneal end are important, and perfect apposition is aimed at. The conjunctiva is sutured as described earlier.

Results

The criterion of success in this study was reduction and maintenance of IOP below 20 mmHg (applanation). This was achieved during the period of observation in 106 eyes (95·4%). In 5 eyes of 4 patients the pressure remained in the range of 21 to 35 mmHg, and these patients were prescribed antiglaucoma drops for maintenance. However, the pressure was never below 21 mmHg except when acetazolamide was added to the regimen.

The visual results were also satisfactory, maintaining the status quo or a line or part of a line less (Tables 4 and 5). It is interesting to note that of those in the PL/CF to 6/60 group no one lost any further vision.

THE BLEB

The beginning of a bleb was seen on the first day in some cases, by third day in most, and in all by the fifth day. On the first weekly visit every case had a well protected flat bleb extending posteriorly. The blebs in those cases with the triangular conjunctivo-Tenon's flaps were fleshy and congested. Some of these proceeded to some encroachment on to the cornea and thin-walled honeycombing along with the flat posterior blebs in a 6-month period. Thin-walled areas were seen in a few cases anteriorly over suture sites in the limbal based conjunctivo-Tenon's cover also. In 1 eye there was no visible bleb when seen at 19 months, with well maintained IOP.

Gonioscopy showed peripheral anterior synechiae of one or both pillars of iridectomy in 14 eyes (12·6%) (Table 6). This did not in any way affect bleb formation or control of IOP. The rest of the angle showed no changes.

COMPLICATIONS

There were no significant complications during or after the operation, nor were complications observed during the period of observation. The minimal complications are shown in Table 7. The one shallow chamber reformed spontaneously on the third day. It was not possible to break the posterior synechiae by medical means. The 1 case of postoperative ocular hypertension was controlled by acetazolamide, phenylbutazone, and atropine and steroid drops, and no further complications occurred in that eye during the observation period.

Discussion

Follow-up of patients is difficult in these areas. However, it was possible to follow up 71% patients for a minimum period of 6 months and a maximum of 19 months. The decision to operate on nearly all these patients was governed by the near impossibility of maintaining them on a medical regimen even though the greatest number of eyes with glaucoma have open angles (Keitzman, 1976; Sandford-Smith, 1978).

Table 6 *Thin-walled blebs and honeycombing*

Nature and site of thin blebs	*Eye/total*	*Percentage*
Anteriorly over suture sites in limbal based conjunctivo-Tenon's cover	5/68	7·35
Corneal encroachment and honeycombing in triangular fornix-based flap	10/43	23·03

Table 7 *Complications*

Nature of complication	*Eyes*	*Percentage*
Conjunctival buttonholing	1	0·9
Shallow chamber	1	0·9
Hyphaema	4	3·6
Posterior synechiae at pupil adjacent to peripheral iridectomy	3	2·7
Peripheral anterior synechiae of pillars of iridectomy	14	12·6
Increased IOP in the immediate postoperative period	1	0·9
Thin-walled blebs and corneal encroachment	15	13·5

Whenever both eyes were affected, they were operated upon at the same time because: (*a*) theatre techniques and surgical refinements and anaesthesia have almost wholly abolished the very remote possibility of losing both eyes from surgical mishaps or infection; (*b*) the patient is spared the duplication of all that is involved in 2 separate operations; and (*c*) there is greater utilisation of hospital beds.

In this series the large number of bilateral surgeries (104 eyes of 52 patients) means that the patients sought treatment late in the disease. However, these bilateral cases form the greater number in the follow-up also, presumably because the patients were keenly aware of the seriousness of bilateral disease, while those with only 1 eye affected became complacent after the successful treatment of that eye.

CONTROL OF INTRAOCULAR PRESSURE

Intraocular pressure was controlled below 20 mmHg in 95·4% of eyes followed up. This has been achieved by following a standardised procedure and without recourse to accessory surgical means, such as excising Tenon's capsule (Welsh, 1972; Keitzman, 1976), non-suturing, loose suturing, or minimal suturing of the scleral flap (Welsh, 1972; Keitzman, 1976; Freedman *et al.*, 1976; Fergusson and MacDonald, 1977; Sandford-Smith, 1978), excision of part of the scleral flap (sclerectomy), iris incarceration (Welsh, 1972), intentional cyclodialysis (Galin *et al.*, 1975), cauterisation of posterior lip and the inner flap (Schimek and Williamson, 1977), very large resection of internal flap of the same measurements as the exterior flap (Keitzman, 1976; Sandford-Smith, 1978), and without recourse to medical measures such as high doses of systemic corticosteroids and/or subconjunctival depot steroids (Fergusson and MacDonald, 1977) and postoperative antiglaucoma medication in those cases not completely controlled (Freedman *et al.*, 1976; Fergusson and MacDonald, 1977; David *et al.*, 1977; Sandford-Smith, 1978). Before this study, such modifications to trabeculectomy procedures were undertaken because of the concept that filtration procedures often produced failures in the African patient (Welsh, 1970).

However, Cassady (1959) did not find sufficient statistical evidence in the literature for failure of filtration operations in the African and advocated a filtering procedure as the first choice in African patients, as did Haas (1958). Chatterjee and Ansari (1972) and David *et al.* (1977) achieved 79·2% and 91·6% success, respectively, with trabeculectomy without accessory procedures in the African. In this

Table 8 *Results of trabeculectomy in African glaucoma patients reported by various authors*

Author	*Procedure*	*Percentage*
Welsh (1972)	With and without sclerectomy, excision of Tenon's capsule, iris incarceration	79·0
Chatterjee and Ansari (1972)	Trabeculectomy alone	79·2
Keitzman (1976)	With excision of Tenon's capsule, excision of large internal flap, of same size and external flap	94·0
Freedman *et al.* (1976)	Non-suturing of scleral flap, postoperative antiglaucoma medication	82·0
Fergusson and MacDonald (1977)	Loose approximation, high steroids, postoperative antiglaucoma medication	84·0
David *et al.* (1977)	With and without antiglaucoma medication	91·0
Sandford-Smith (1978)	Non-suturing, minimum suturing, large excision of internal flap same size as external flap	87·0
Schimek and Williamson (1977)	Cautery of posterior lip and posteriorly of inner scleral layer	83·0
Present authors	Standardised trabeculectomy only	95·4

study control of IOP was observed in 95·4% of the eyes after a standardised operation, and there was no postoperative antiglaucoma medication or steroids. The results of this study and those of various authors in African glaucoma population are shown in Table 8.

The reduction in pressures was substantial, and it had no particular relation to initial pressures or age or sex of patients. Even though a few patients had low pressures (below 8 mmHg), no complications were noted during the period of observation (Keitzman, 1976). The uncontrolled eyes were not amenable to topical antiglaucoma medication except when it was combined with acetazolamide.

The inclusion in this study of the group PL/CF to 6/60 has shown (contrary to the usual practice at least so far as other filtering procedures are considered) that trabeculectomy is safe even in these types of cases when one is confronted with the problem of what is the most humane way of treating such cases (and there are many of them in this area). In this study the pressure was reduced in all except 1 patient (2 eyes), and no one's sight became worse after operation. It is hoped that they will maintain what vision they have for a longer period than they would have done if they had not been operated upon.

The cause of raised IOP in the immediate postoperative period in 1 case is not known. But it was quickly controlled by acetazolamide and phenylbutazone orally, and atropine and steroid drops topically. This patient has maintained an average of 20 mmHg so far.

The immediate and long-term control of IOP in this study may be due to the following factors. (1) Minimum postoperative inflammation and therefore no damage in the filtration angle. (2) Absence of shallow chamber, which is the most important single criterion (Schwartz and Anderson, 1974). This is achieved by the superficial scleral flap of more than two-thirds thickness which is sutured securely so that the anterior chamber has not been lost at any time (Rodriques *et al.*, 1978). (3) Adequate filtration effected by a large superficial flap; a moderately large trabeculectomy (3×3 mm), producing an adequate hiatus from the anterior chamber; adequate exposure of ciliary body beyond the scleral spur for easy egress of aqueous (Galin *et al.*, 1975); a broad-based iridectomy, minimising the chances of synechiae; and the use of pilocarpine immediately after iridectomy to prevent peripheral anterior synechiae.

MECHANISM OF DRAINAGE

Trabeculectomy functions mainly as a filtration procedure (Ridgway, 1974; Galin *et al.*, 1975). The mechanism of filtration may work in the following ways.

(1) Drainage into the conjunctivo-Tenon's space via (*a*) corneoscleral incisional sites (Kwitko, 1973), particularly through the corneal end, because the earliest sign of bleb formation is seen at this site; (*b*) the suture tracts, first by capillarity and later through the tracts (the sutures of superficial scleral flap are through-and-through and rest on the ledges of the posterior flap on 3 sides); (*c*) the exposed intrascleral drainage channels of the large superficial flap (Kwitko, 1973).

(2) Suprachoroidally (Kwitko, 1973), which must be minimum, because there is practically no cyclodialysis having a ledge of posterior scleral flap on 3 sides and because of the absence of choridal detachments and shallow chambers.

(3) Through the cut ends of Schlemm's canal, which is also probably minimal (Thyer and Wilson, 1972).

(4) A combination of all the above mechanisms.

That trabeculectomy is a safe procedure with almost no complications (Watson and Barnett, 1975) is confirmed in this study also. The virtual absence of complications in this series of trabeculectomies may be attributed to the thick superficial scleral flap and its being sutured securely (Rodriques *et al.*, 1978) and to the minimum of instrumentation.

Thus, the low incidence of hyphaema may be due to the selection of a site devoid of large vessels, particularly the perforating anterior ciliaries; the careful dissection of the posterior flap, avoiding injury to the ciliary body; avoiding injury to ciliary processes during iridectomy; immediate use of pilocarpine after iridectomy, which will keep the iris taut, compressing the vessels; the thick scleral flap, which gives pressure and protection; the secure suturing of the scleral flap (Freedman *et al.* (1976) had more hyphaema with unsutured flaps); the quick reformation of anterior chamber, keeping up an average IOP.

The near absence of shallow chambers must be directly attributed to the thick scleral flap and the secure closure of the same (Warmock, 1977; Rodriques *et al.*, 1978).

The posterior synechiae of 2·7% may be because of the surgical trauma to the iris (these cases had the largest iridectomies) and the use of pilocarpine.

The absence of cataract from trabeculectomy in this series might be because of the minimal surgical trauma and inflammation; no loss of and quick reformation of anterior chamber; minimal instrumentation (pilocarpine is used to draw the iris into the chamber rather than its being reposited by an iris repositor); and the slow release of aqueous by a gradual iridectomy.

The formation of thin-walled honeycombing was seen in the semi-fornix-based triangular flaps and also the limbal-based conjunctivo-Tenon's flap. In both this occurred anteriorly at the corneal end of the corneoscleral incisions and over suture sites when virgin silk was used instead of absorbable sutures. This therefore can be avoided by meticulously suturing the corneal ends of the incisions and using absorbable sutures. In this series we have found that 8/0 Vicryl is the best suture because of its fineness, manoeuvrability, knot security, and absorbability.

FILTRATION BLEBS

It was found that for a draining bleb it is not necessary in the African patient to excise the Tenon's capsule (Welsh, 1972; Keitzman, 1976). To do so would increase the risk of thin-walled blebs, with possible chances of injury and infection. Nor is it necessary to leave the scleral flap unsutured or minimally sutured (Freedman *et al.*, 1976; Fergusson and MacDonald, 1977; Schimek and Williamson, 1977; Sandforth-Smith, 1978), to resort to combined sclerectomy or iris inclusion procedures (Welsh, 1972), to cauterise heavily the posterior lip and posterior lamella (Schimek and Williamson, 1977), or to administer systemic steroids to prevent fibrosis. Such procedures may increase the hazard of overdrainage, non-formation, and shallow chambers, which in turn would cause peripheral anterior synechiae and reduce the success rate.

The attempt in this study was to consider the African patient as any other glaucoma patient and to do the trabeculectomy in a standardised way, with care being taken to produce a well controlled drainage mechanism. With these aims all other forms of surgical treatment, as mentioned above, were avoided, and a thick superficial flap was fashioned and at the end of operation was securely sutured. These techniques have, in particular, avoided shallow chambers and produced controlled drainage consistently (Warmock, 1977; Rodriques *et al.*, 1978). They have also prevented staphylomas (Spaeth and Rodriques, 1977) and infections or endophthalmitis (Freedman *et al.*, 1978).

In this series a bleb, present sometimes on the first postoperative day and in all cases by the fifth day, possibly appears at the corneal end of the incisions, because in its earliest stages it is first noticed at these sites, perhaps in the same way as some filtration occurs after cataract incisions (Swan and Campbell, 1964). It is noteworthy that thin-walled blebs over sutures and in triangular conjunctivo-Tenon's flaps occurred at these anterior corneal incisional sites. Because of this, it is important to suture these anterior corneal incisions with special care.

The presence of a bleb was always associated with a well controlled IOP except in 1 eye with well controlled IOP in which no visible bleb was seen 19 months after operation (Ridgway *et al.*, 1972; Freedman *et al.*, 1976). The corneal encroachment with the triangular flaps may be prevented by more careful suturing at the limbus (Table 9).

It is not necessary to identify the Schlemm's canal or trabecular tissue and excise it for a successful trabeculectomy (Schwartz and Anderson, 1974; Galin *et al.*, 1975). Histopathological study has shown 85% identification of Schlemm's canal and/or trabecular tissue.

MAGNIFICATION IN TRABECULECTOMY

Trabeculectomy has been made possible because of the more widespread use of the operating microscope, and the results from microsurgery of trabeculectomy are excellent in the hands of surgeons who are using the operating microscope routinely for most ophthalmic surgery. However, microsurgery

Table 9 *Advantages and disadvantages of the two types of conjunctivo-Tenon's flaps*

	Advantages	*Disadvantages*
1. Classical limbal based	1. Blebs are well contained and never encroach on the cornea	1. Buttonholing and tearing, especially in older patients with thin conjunctiva
	2. Closure easier and secure	2. The reflected flap over the cornea precludes constant view of superior cornea and pupil
2 Triangular semi-fornix based	1. No buttonholing or tearing	1. Suturing has to be more meticulous
	2. Perfect exposure of operative area and view of whole chamber and pupil	2. A tendency for the bleb to encroach on cornea and thinning at these sites

However, the surgical results were equal with both types of conjunctivo-Tenon's flaps

in the hands of the occasional microscopist is not good enough. Advantageous as it is, the operating microscope is not essential for trabeculectomy. A magnification 2·5 times is sufficient for a properly and carefully executed trabeculectomy, as shown by this study, in which an operating loupe of 2·5 times was routinely used with excellent results. This means that trabeculectomy is within the capacity of the average ophthalmic surgeon to the great benefit of glaucoma sufferers, for the operation has proved to be the method of choice par excellence in the surgical management of glaucoma in both the African and the white races (Ridgway *et al.*, 1972; Freedman *et al.*, 1976; David *et al.*, 1977).

Conclusions

The high rates of success and virtual absence of complications in this series of cases indicate that trabeculectomy functions as well in African patients with glaucoma as in the white races or even better. Trabeculectomy should be the method of choice in the surgical management of open-angle glaucoma irrespective of the patient's race.

We are grateful for the co-operation extended to us by the consultants, residents, nursing, and secretarial staff of the Guinness Ophthalmic Unit.

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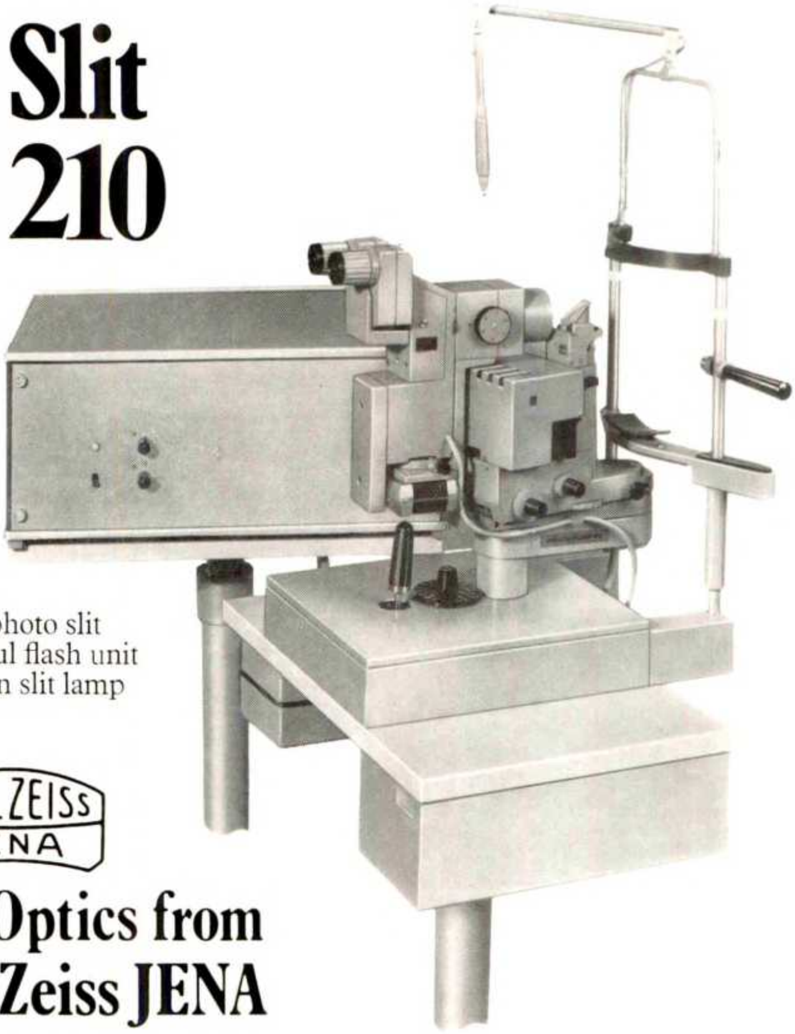

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Trabeculectomy versus Scheie's operation: a comparative retrospective study in open-angle glaucoma in Kenyans

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SUMMARY A comparative retrospective study was performed on 39 patients with open-angle glaucoma in whom the right eye was subjected to Scheie's operation, the left to trabeculectomy. Trabeculectomy without the use of additional therapy or reoperation brought the intraocular pressure to under 22 mmHg in 80% of the cases compared with 74% treated by Scheie's operation. Reduction of visual acuity postoperatively was 4 times more frequent with Scheie's operation than with trabeculectomy. A report on a second group of patients in whom 47 trabeculectomies were performed is also given.

In the majority of Kenyan patients with open-angle glaucoma conservative treatment is out of the question, as irregular supplies of drugs, inconstant application, and insufficient follow-up make it unlikely to succeed. Therefore filtration surgery is the rule when visual field loss is observed. Although the first reports on trabeculectomies in black populations were conflicting (Chatterjee and Ansari, 1972; Welsh, 1972) more recently Freedman *et al.* (1976) and David *et al.* (1977) described good results in 80 and 91·6% of their cases respectively. In considering results of any kind of surgery, apart from the particular technique used, other factors have a role, such as the proficiency of the surgeon, the social class of the patient, and the quality of the postoperative treatment and care.

The usual method of filtration surgery in the Kenyatta National Hospital in Nairobi was Scheie's procedure. Before introducing trabeculectomy we considered a comparative study in the local situation was required, the results of which are reported here together with those of a study solely of trabeculectomy. These results may be a guideline for eye surgeons in most developing countries.

Materials and methods

In contrast to other studies the open-angle glaucoma in our patients is not necessarily uncontrolled. As conservative treatment was doomed to failure, patients with open-angle glaucoma seen between February 1975 and September 1977 who showed visual field loss and in whom bilateral surgery was advisable were subjected to Scheie's operation in the right eye and trabeculectomy in the left eye.

There were 48 patients in this first group, 9 of whom were excluded because the follow-up was less than 3 months. The remaining 39 were Kenyan Africans, 31 males and 8 females. The age of the patients varied from 20 to 75 years, with a mean of 55·4 years. Follow-up was from 3 to 26 months, with a mean of 11·8 months. The second group consisted of patients for whom bilateral surgery was not indicated or for whom enthusiastic but unbiased surgeons did a trabeculectomy on both eyes. In this group 77 operations were performed, 47 of which, on 33 patients, could be followed up for a minimum of 3 months. Again all were Kenyan Africans, 21 males and 12 females, varying in age from 25 to 73 years with a mean of 51·7 years. The follow-up was between 3 and 33 months, with a mean of 19·6 months.

In the first group only primary surgery was performed. In the second group 4 failures of earlier filtration surgery were included. All patients were phakic. Postoperatively all intraocular pressures were measured with an applanation tonometer by the first author.

The technique used for Scheie's operation was as described by Scheie (1958). Trabeculectomy was performed as indicated by Cairns using the modification given by Watson (1972). Magnification of ×2 was used in the trabeculectomies. All operations were performed under local anaesthesia. Patients were mobilised on the first postoperative day and discharged on the fifth. Post operative treatment consisted of antibiotic, steroid, and cycloplegic eye ointment 3 times a day.

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The intraocular pressure was considered controlled when it was below 22 mmHg at the latest visit without additional medication. The visual acuity was recorded as worse when, in comparison with the preoperative level, there was a drop of 2 or more lines on Snellen's chart or of steps in the range 6/60, 5/60 to 3/60, 2/60 to 1/60, hand movements, perception of light, and no perception of light.

Results

Table 1 presents the results of group 1, that is, the comparative study between Scheie's operation and trabeculectomy, as well as those of group 2, the trabeculectomy-only group. The mean intraocular pressure postoperatively has been divided into 2 groups, those that were controlled and those that were not.

In group 1, out of the 39 eyes subjected to Scheie's operation 9 had a flat anterior chamber for more than 3 days, resulting in uncontrolled pressures in 2 eyes and in lowered sight in 3. In 3 eyes treated by this operation a hyphaema occurred, resulting in 2 failures, 1 ending in endophthalmitis. One eye on this operation needed repair of a leaking bleb 3 months after the operation. In the 39 eyes treated by trabeculectomy a flat anterior chamber lasting a week caused a drop in visual acuity. One eye had vitreous loss, causing the visual acuity to diminish and leaving the pressure increased. In 47 eyes in group 2 treated by trabeculectomy there were 2 cases of hyphaema which cleared without sequelae.

Table 1 *Intraocular pressure with standard deviation in mmHg pre- and postoperatively and results of surgery in groups 1 and 2*

	Group 1		*Group 2*
	Scheie's	*Trabec.*	*Trabec.*
Number of operations	*39*	*39*	*47*
IOP preop.	34·9±9·1	33·8±10·0	33·4±6·7
IOP postop.			
(controlled)	13·6±5·0	16·2±3·4	15·7±2·4
(uncontrolled)	31·8±6·3	28·1±7·2	30·7±2·9
IOP controlled (<22 mmHg)	29 (74%)	31 (80%)	40 (85%)
Visual ac. same or better	31 (80%)	37 (95%)	41 (87%)

Table 2 *Change in intraocular pressure between 3rd and 15th month after surgery (mmHg ± SD)*

	Group 1		*Group 2*
	Scheie's	*Trabec.*	*Trabec.*
Number of operations	*6*	*10*	*19*
IOP at 3 months	11·7±4·6	14·4±6·5	18·2±2·5
IOP at 15 months or later	10·8±6·1	15·4±4·4	15·9±2·5
Change in mean IOP	–0·9	+1·0	–2·3

Vitreous loss occurred in 2 eyes, 1 of which lost sight and ended with high pressure.

In patients with controlled intra-ocular pressure who could be followed up for 15 months or longer and for whom sufficient data were available the course of intraocular pressure was followed. Table 2 gives the change in mmHg between visits at 3 months approximately and at 15 months or more postoperatively.

Discussion

When, as in the second group, 27 out of 77 operations have a follow-up period of less than 3 months, or sometimes no follow-up at all, the question is whether it was the failures or the successes who did not return. Seventy-six patients who seldom, if ever, turned up for control visits were invited by letter to report to the glaucoma clinic, from which request we had almost a 50% response. Eighteen of those fell into the Scheie—trabeculectomy group. The pressures were regulated in 72% and the visual acuity was as before or better in 80%. In the trabeculectomy group 18 patients, altogether 21 operated eyes, had a regulated pressure in 90% and no decreased visual acuity in 85%. Although again the fate of those who did not reply was unknown, it became more likely that they had either died or could not afford the transport costs to the hospital.

There is little reason to believe that in this study defaulting influenced the results. Whether acceptance of a minimum follow-up of 3 months would be sufficient was investigated by comparing the intraocular pressures at postoperative control visits at 3 months and 15 months or more. For the Scheie's operations as well as for the trabeculectomies, fluctuations were limited to a few mmHg. Again, of the total of 23 eyes in this study in which ultimately the pressure was not controlled the failure was found within 3 months in 19 eyes. In 2 patients it was noticed at their first visit at 6 months after surgery and in only 2 was it detected at 12 months.

Having dealt with the most obvious reasons for incorrect interpretation of the results, we can consider the main object of this study. In a comparative study Scheie's procedure controlled the intraocular pressure in 74% of the cases versus 80% in trabeculectomy. The difference is insignificant, and there would be little reason for preferring one procedure to the other had it not been shown that patients after Scheie's operation have a 4 times higher risk of ending with a decreased visual acuity postoperatively, mainly due to lens opacities. We believe there is a difference between the cases in which postoperatively increased intraocular pressure is due merely to insufficient drainage and those in which the problem is caused by surgical complications. The latter accounted for 4 out of 10 uncontrolled intraocular pressures in eyes treated by Scheie's operation, for 1 out of 4 trabeculectomies in group 1, and for another 1 out of 7 in those in group 2. The higher failure rate that consequently can be expected in repeat surgery may be another reason for selecting trabeculectomy in preference to Scheie's operation.

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Ocular changes in rabbits with corticosteroid-induced ocular hypertension

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SUMMARY Rabbit eyes with steroid-induced ocular hypertension were investigated in order to evaluate the histochemical abnormalities in the chamber angle region. The right eye of 14 rabbits was treated by dexamethasone 1% 3 times daily for 3 to 5 weeks. The eyes were stained by haematoxylin-eosin, periodic acid Schiff, fibrin, colloidal iron, and alcian blue with and without hyaluronidase. All treated eyes developed elevated intraocular pressure up to 4 weeks after treatment. These globes showed alcian-blue-positive hyaluronidase-sensitive staining in the amorphous material adjacent to Schlemm's canal and in the cytoplasmic granules of trabecular endothelial cells. There was no increase in incorporation of radioactive thymidine into nuclei of endothelial cells as seen by autoradiography. These results provide further support for the idea that there is abnormal accumulation of acid mucopolysaccharides in the chamber angle in steroid-induced ocular hypertension.

Steroid-induced ocular hypertension is a well-known clinical problem which at times leads to optic nerve damage and blindness (Armaly, 1963; Becker and Hahn, 1964). In contrast to open-angle glaucoma the existence of an animal model for this disease makes it possible to investigate its pathogenesis by various approaches (Podos, 1976). It has been previously shown that transient increase in intraocular pressure can be induced in rabbits by topical corticosteroid therapy (Tuovinen *et al.*, 1966; Wood *et al.*, 1967; Brown and Geeraets, 1972; Levene *et al.*, 1974; Podos, 1976. However, the mechanism of this phenomenon has not been elucidated. Routine histopathological examination did not reveal any abnormalities in the anterior chamber angle (Levene *et al.*, 1974), yet some biochemical changes in the aqueous humour were found (Virno *et al.*, 1974; François and Victoria-Troncoso, 1974).

Recently much attention has been given to the possible role of biochemical abnormalties such as accumulation of mucopolysaccharides in the formation of steroid-induced glaucoma (François and Victoria-Troncoso, 1974; François, 1975). The purpose of the present study was to evaluate further the possible histochemical abnormalities in the chamber angle of rabbits with ocular hypertension induced by topical corticosteroids.

Materials and methods

ANIMALS

Fourteen age-matched female albino rabbits weighing approximately 2 kg were tested. They were kept in separate cages in animal room conditions. The rabbits were fed Purina and drank water freely. No ocular abnormalities could be found on external and slit-lamp examination prior to the beginning of the experiment.

TREATMENT

The right eye of the 14 rabbits was treated 3 times daily by 1% dexamethasone eye drops while the left eye served as control. Dexamethasone sodium phosphate (Merck Sharp & Dohme) was dissolved in phosphate buffer to a final concentration of 1% at pH 7·4. The intraocular pressure was measured at noon twice a week by both the Mackay-Marg and a modified Schiotz tonometers. The animals' weights were recorded simultaneously. Six animals were killed at 3 weeks, 6 animals at 4 weeks, and 2 more 5 weeks after the beginning of treatment.

HISTOLOGY

The eyes were enucleated and fixed in 10% buffered

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formalin. All eyes were processed for paraffin embedding and later 4 to 6 μm sections were cut. From each globe sections were stained by haematoxylin and eosin, periodic acid Schiff, fibrin, colloidal iron, and alcian blue stains with and without bovine testicular hyaluronidase. The intensity of the staining was graded as – when no reaction was seen; ± when only faint stain could be identified; + when definite positive stain of tissue was present, and ++ when a strong reaction was seen.

AUTORADIOGRAPHY

In 3 animals of the first and second group and 2 of the third group paracentesis of both eyes was done and 0·1 ml of aqueous was drained. Through the same needle 0·1 ml of tritiated thymidine (KMG-Israel) at final activity of 0·2 μCi was injected into the anterior chamber. The needle was withdrawn and the puncture site plugged. Three hours later the animals were killed, and the eyes were fixed in 10% buffered formalin and processed for paraffin embedding. These eyes were later deparaffinised, dipped in Kodak NTB 2 emulsion, and developed 2 to 4 weeks later for autoradiography.

Results

It is evident that in the present study all treated eyes developed raised intraocular pressure as compared to control eyes (Table 1). The pressure was equal in both eyes during the first week of treatment, in the second week increased an average of 4 mmHg, and in the third week further increased to 9 mmHg above control levels. In the fourth week of treatment the pressure levels began to decline. In the control eyes there was a non-significant rise of 1 to 2 mmHg on repeated measurements. A statistical analysis by the paired *t* test showed the results to be highly significant.

Table 1 *Mean IOP of rabbits during 1% dexamethasone treatment*

	Weeks	*Mean*	*SD*	N	t		*P value*
	Treated right eye						
1	0	12·21	0·83	14	1:2	9·48	< 0·001
2	1	17·46	1·80	14	2:3	5·95	< 0·001
3	2	22·79	3·21	14			
	Untreated left eye						
1	0	12·18	0·67	14	1:2	2·92	0·012
2	1	12·89	0·84	14	2:3	2·03	0·06
3	2	13·39	0·68	14			

Table 2 *Mean weights of rabbits treated by 1% dexamethasone eye drops*

	Weeks	*Mean*	*SD*	N	t		*P value*
1	0	2·385	0·568	14	1:2	4·05	0·001
2	1	2·268	0·536	14	2:3	3·54	0·004
3	2	2·175	0·518	14			

Weight loss continued during the treatment period, in particular during the second week after treatment (Table 2). Histopathological examination of sections stained by haematoxylin-eosin revealed vacuolisation and oedema of the trabecular endothelial cells more frequently in the treated eyes. Fibrin stain was faintly positive in 8 treated eyes and 2 untreated eyes. The fibrin stain was not consistent and was usually associated with a small haemorrhage in the area. Periodic acid Schiff positive material was present in 8 treated and 6 untreated eyes. It was usually located extracellularly in close association with trabecular endothelial cells. Colloidal iron stain showed faintly positive granules in 11 treated and 5 untreated eyes. This reaction was seen mainly in endothelial cells of the trabecular meshwork, the amorphous material of the interstitial space, and in close proximity to Schlemm's canal.

Alcian-blue-positive staining, which partially disappeared after treatment with hyaluronidase, was present in the treated and untreated eyes. However, it was seen more often and was more intense in eye treated by steroids (Table 3). This staining was noted as amorphous material in the intertrabecular spaces and adjacent to Schlemm's canal. In addition alcian-blue-positive intracellular granules were noted in the cytoplasm of endothelial cells (Figs. 1, 2). The most positive reaction in steroid-treated eyes was seen 3 to 4 weeks after the beginning of therapy. However, a faint reaction was present in untreated eyes as well (Fig. 3).

The autoradiographic sections showed almost no grains over the nuclei of the trabecular meshwork in either the treated or the untreated eyes. It is interesting to note that in the steroid-treated eyes larger numbers of labelled cells were seen in the conjunctival and corneal epithelium, the iris melanocytes, and within the endothelial cells of iris blood vessels.

Discussion

No good experimental model of primary open-angle glaucoma is yet available; consequently, investi-

Table 3 *Histopathological findings*

No.	*Week*	*H and E*		*PAS*		*Colloidal iron*		*Alcian blue hyaluronidase sensitive*	
		R	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1	2	*N*	*N*	±	+	±	−	±	−
2	2	Oedema	Vacuoles	±	±	±	−	+	±
3	2	*N*	*N*	−	−	+	±	±	±
4	2	Oedema	Vacuoles	[illegible]	−	+	±	+	±
5	2	Vacuoles	Vacuoles	±	++	−	−	++	−
6	2	*N*	*N*	−	−	±	−	++	±
7	3	Vacuoles	*N*	±	−	+	[illegible]	±	+
8	3	Oedema	*N*	[illegible]	−	±	−	±	±
9	3	*N*	*N*	−	−	−	−	− +	±
10	3	Vacuoles	*N*	[illegible]	−	+	[illegible]	+	+
11	3	Vacuoles	*N*	[illegible]	−	[illegible]	[illegible]	++	+
12	3	*N*	*N*	[illegible]	−	±	−	±	−
13	4	*N*	*N*	−	−	−	−	±	±
14	4	Vacuoles	*N*	±	±	±	−	+	±

N = no pathological findings.

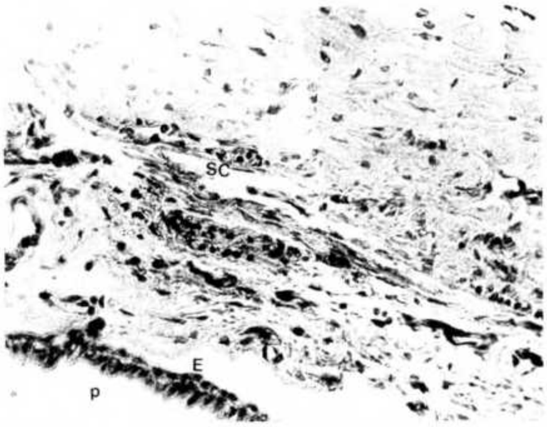

Fig. 1 *Chamber angle of the steroid-treated right eye. Alcian-blue-positive hyaluronidase-sensitive material is seen as dark-stained granules in the filtration area and adjacent to Schlemm's canal (SC).* E = *detached ciliary epithelium;* P = *posterior chamber. Alcian blue,* × *40*

gations into the pathogenesis of the disease are rather limited (Podos, 1976). However, steroid-induced elevation of intraocular pressure, which is a well-established clinical entity, can be reproduced to some extent in experimental animals (Armaly, 1964; Wood *et al.*, 1967; Brown and Geeraets, 1972; Levene *et al.*, 1974). In the present study, as in previous studies, the rabbit eyes which were treated by topical steroids developed a significant pressure rise 2 to 3 weeks after the commencement of therapy accompanied by systemic weight loss (Wood *et al.*, 1967; Levene *et al.*, 1974). The mechanism which lies behind that rise in intraocular pressure is still debateable. Routine histopathological studies did not reveal any abnormalities (Wood *et al.*, 1967). At times pressure-related vacuoles in the endo-

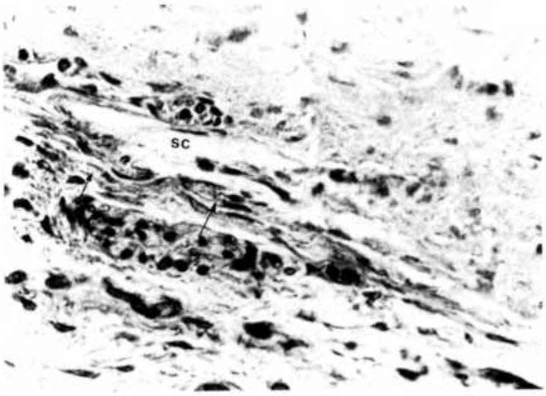

Fig. 2 *Higher magnification of the same area. The alcian-blue-positive material is seen intra- and extra-cellularly and in the juxtacanalicular tissue (arrows). SC* = *Schlemm's canal. Alcian blue,* × *360*

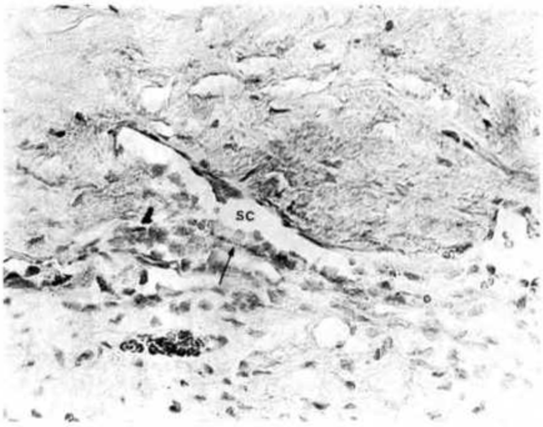

Fig. 3 *Filtration region in an untreated eye. Only a few alcian-blue-positive granules are seen in the juxtacanalicular area (arrow). SC = Schlemm's canal. Alcian blue, × 360*

thelium of Schlemm's canal could be seen (Tripathi, 1972; Johnstone and Grant, 1973), yet in the light microscopic study we had the impression that vacuoles or endothelial swelling could be identified more often in the treated eyes.

In an attempt to evaluate the cellular function in short-term experiments by thymidine uptake no connection between nuclear morphology or function and the moderate elevation of intraocular pressure was found. It seems as if the cells of the trabecular endothelium are rather stable, and therefore no short-term incorporation of tritiated thymidine into those nuclei could be observed with or without steroids.

In the present study intra- and extracellular accumulations of hyaluronidase-sensitive acid mucopolysaccharides were seen in both treated and untreated eyes. However, it was our impression that these were present to a greater degree in the treated eyes. Since it was first described, these substances have been repeatedly identified in the filtration area (Segawa, 1971; Armaly and Wang, 1975).

Some reports claim that trabecular endothelial cells in tissue culture secrete mucopolysacchardies. Further characterisation of this substance by histochemical methods indicates that the non-fibrillar material which corresponds to the glass membrane and elastic fibres in the corneoscleral meshwork contains chondroitin sulphate protein complex and glycoprotein. This material, which stains PAS positive, increases in thickness with age and is not related to increased intraocular pressure in man. On the other hand the amorphous material underneath the endothelial wall of Schlemm's canal is hyaluronidase-sensitive and is present in large quantities when the outflow facility is reduced (Segawa, 1975). In addition physiological data support this observation, since perfusion experiments indicate that the outflow facility increases temporarily with hyaluronidase (Barany and Woodin, 1955; Berggren and Vrabec, 1957). Moreover, it was previously suggested that patients with primary open-angle glaucoma have increased sensitivity to topical steroids (Armaly, 1963; Becker and Mills, 1963; Becker, 1965). It can be speculated, therefore, that increased amount of acid mucopolysaccharides in an already susceptible eye may be responsible for an increase in outflow resistance which is induced by topical steroids (Armaly and Wang, 1975; François, 1975). The present study supports the observation that such accumulations are seen in the chamber angle affected by topical steroids. The exact mechanism of this accumulation is not clear, yet it may be related to the inhibition of lysosomal enzymes, which are responsible for the degradation of mucopolysaccharide-protein complexes (Dingle and Fell, 1969). These findings suggest that the abnormal metabolism of this material may be involved in some of the mechanisms which lead to increased intraocular pressure, even though a direct cause-and-effect relationship remains to be established.

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Book reviews

Handbook of Clinical Ultrasound. Eds. MARINUS DE VLIEGER, JOSEPH H. HOLMES, ALFRED KRATOCHWIL, EKKEHARD KAZNER, ROBERT KRAUS, GEORGE KOSSOFF, JACQUES POUJOL, and D. E. STRANDNESS. Pp. 970. £42·50. John Wiley: Bognor Regis. 1978.

This book is divided into 8 sections, each containing several chapters. The first, entitled 'Basic Principles', contains a historical account of the use of ultrasound in medicine and the basic physical principles of ultrasonic diagnosis. Features of transducers are covered with great clarity, followed by a discussion of some pulse-echo techniques together with technical considerations in design of diagnostic equipment. A very worthwhile chapter is then devoted to the principles of grey scale echography, together with its applications; the best quality ophthalmic B-scans in the book are to be found in this chapter. Artefacts and standardisation techniques are described in the following 2 chapters. Next, transducer arrays and the relatively new application of computers to diagnostic ultrasound are discussed in a way the ophthalmologist can understand. Interesting chapters are then devoted to the principles of Doppler ultrasound together with scattering and attenuation of ultrasound by tissue. Finally, the biological effects and safety of ultrasound are considered. Thus, the first section of this book provides a comprehensive guide for the ophthalmologist working in ultrasonic diagnosis.

Other sections are devoted to Doppler techniques and ultrasonic diagnosis in obstetrics and gynaecology, internal medicine, cardiology, neurology, and orthopaedics. The penultimate section of the book deals with diagnostic ultrasound in ophthalmology. This section begins with a lengthy article on so-called 'specialised' techniques, and many statements are controversial. It is hardly surprising, however, that the author feels grey-scale B-scanning is inadequate for observing echo amplitude when we see the very poor quality of the grey scale on B-scans presented in the third and fourth chapters of the section. These chapters are devoted to retinal and choroidal detachment and intraocular tumours, respectively. The authors of chapter 3 refer only to their own work in the list of references, while the author of the chapter on intraocular tumours states that macular melanomas are very rare (claiming to have seen only 3 cases in 14 years). In contrast, biometric studies are comprehensively covered in chapter 2, while the fifth chapter contains a practical and objective discussion of the role of diagnostic ultrasound in injuries due to foreign bodies. In the chapter on orbital disorders the author strongly advocates the use of A-scan rather than B-scan and make other controversial judgments. It is claimed, for example, that the A-scan technique should be used to measure the true diameter of the optic nerve and extraocular muscles. Anatomically, however, it is impossible to direct the sound beam so as to strike these structures perpendicularly and permit such measurements (even with deviated gaze). The author also claims that by his method an experienced examiner can expect to detect or eliminate an orbital lesion in 98% of cases, and in 99% of cases the diagnoses made are correct. Finally, the ophthalmology section closes with an interesting chapter on the use of Doppler techniques in diagnostic ophthalmology.

Overall, the ophthalmic section of this book is disappointing. However, the ophthalmologist will benefit from reading the first section of the book. MARIE RESTORI

Microsurgery of the Vitreous. By RICHARD M. KLEIN and HERBERT M. KATZIN. Pp. 153. $27·50. Williams and Wilkins: Baltimore, Maryland. 1978.

The authors' stated intention was to create a book quite different from others on vitreous microsurgery by comparing critically the latest surgical techniques, instrumentation, and philosophy. Unfortunately the first section, which considers the normal and pathological vitreous and previtrectomy evaluation of cases, conforms to the pattern of other recent vitrectomy manuals but falls well below their standard. The selection of material is arbitrary and fails to orientate the 'vitreous neophyte' meaningfully to the practical material which follows. The short chapter on the normal vitreous, for example, concentrates on biochemical rather than microanatomical aspects of structure, and left the reviewer in some bewilderment by claiming that it is the central part of the gel, rather than the cortical gel, which is the most viscous and has the highest collagen content. Similarly, in the chapter on vitreous pathology animal models of vitreous disease, some of which have dubious or unproved clinical relevance, are emphasised to the virtual exclusion of essential surgical pathology; we are given no clear statement, for example, as to the nature of the various types of vitreoretinal traction.

By obtaining the views of surgeons experienced in the use of several vitrectomy instruments the authors attained a qualified measure of success in section 2, which is designed to help the aspiring vitrectomist answer the question, Which instrument shall I buy? The authors concede, however, that there is no ideal instrument, and what is an advantage to one surgeon is a fault to another—witness the view that the Ocutome is 'too small'. Nevertheless, the interviewing technique allows the views of some of the most experienced and innovative surgeons, whose opinions otherwise seldom appear in print, to be given an airing. The chapter on ancillary modalities in vitreoretinal surgery is also quite useful, though ophthalmologists in the United Kingdom cannot fail to be amused by summary dismissal of liquid silicone injection despite the fact that combined vitrectomy and silicone oil injection procedures are likely to assume a greater and greater importance in the management of the severest vitreoretinal problems.

By the third section, which deals with the indications and complications of vitreous surgery together with published results, the authors' style of reporting tends to irritate, the same emphasis being given to anecdotal observation and hard statistics. This section does, however, provide a useful bibliography of material published up to 1977. The final section, which considers the future of vitreous surgery and current controversies, was rather more readable though the questions asked were somewhat naive and the answers proffered generally unimaginative. All in all this book is disappointing. DAVID MCLEOD

Eye Movements and the Higher Psychological Functions. Ed. JOHN W. SENDERS, DENNIS F. FISHER, and RICHARD A. MONTY. Pp. 394. £21·00. John Wiley: London. 1978.

This volume reports the proceedings of a conference held in February 1977 in Monterey, California. The conference was the second on this subject, the proceedings of the first having been published in 1976.

It is in some ways refreshing to relate the cerebral control of ocular movements to the higher visual functions for which they have been developed. This also introduces a practical element which some of the recent volumes on eye movements have omitted in their concentration on the neurophysiological, neuroanatomical, or biomedical aspects of the control of eye movements. Thus the reader who does not possess an up-to-date account of eye movement control is gently introduced by Robinson and Goldberg to the visual substrate of eye movements. This platform enables him to delve deeper into saccadic suppression, the role of eye position in space perception, and the co-ordination of eye movements in perception.

A whole section is devoted to eye movements in the process of reading, and this is followed by a section on eye movements in looking at static and dynamic displays. Searching for NINA (after Hirshfeld) emphasises the pattern of eye movement search when the subject is asked to find the word NINA camouflaged in a picture. The final section discusses recordings of eye movements to assess patterns of search used in driving a car and analysing a chest *x*-ray.

This volume provides ophthalmologists with further information on the complex motor and sensory integration occurring in the brain and subserving the visual organ, whose function he strives to maintain. It is worthy of perusal by those interested in broadening their knowledge, and the extensive bibliography provides an opportunity to delve more deeply. M. D. SANDERS

Goniodysgenesis: A New Perspective on Glaucoma. By TORD JERNDAL, HANS ARNE HANSSON, and ANDERS BILL. Pp. 212. DK300. Scriptor, Copenhagen: 1978.

It is the authors' hypothesis that the fenestration of the primitive endothelium lining the anterior chamber and the subsequent development of the angle recess may be arrested or disturbed by either genetic or environmental agents, thus producing a condition of goniodysgenesis and creating the mechanical prerequisites for a block at the pretrabecular level. They are led to this conclusion from a study of the embryology of the normal angle, on which there is a chapter, and by consideration of the physiology of the healthy iridocorneal outflow. Their method of investigating eyes with glaucoma is by correlating gonioscopic findings with those from the scanning electron microscope, examining tissues removed at trabeculectomy and sometimes post-mortem specimens of whole eyes. They recommend gonioscopy with the Haag-Streit 900 slit lamp, using a distinctly narrow slit with extra eye pieces (×16).

Congenital glaucoma is regarded as a rare and maximal expression of goniodysgenesis with the presence of a Barkan membrane. They believe that the true genetic trait in congenital glaucoma is goniodysgenesis, resulting in a dominant (sometimes markedly irregular) hereditary pattern. The close association of infantile congenital glaucoma and juvenile and adult open-angle glaucoma in the same family is to them a clear indication that a similar aetiology is probably at work in all three, and their aim is to convince the reader that this is proved.

Since dysgenesis of the iridocorneal angle is the primary cause of congenital glaucoma, it is only natural to find other signs of maldevelopment in many of these glaucomatous eyes, particularly in the anterior segment. All these anterior malformations have an autosomal dominant inheritance. In this light the authors discuss various keratodysgeneses such as opacification of the cornea and sclerocornea, ruptures of Descemet's membrane, anomalies of the corneal diameter, and embryotoxon; iridodysgeneses such as aniridia, colobomas, persistent pupillary membrane, and hypoplasia of the iris stroma; phacodysgeneses such as cataract and congenital dislocation of the lens; and complex dysgeneses of the anterior ocular segment, including Reiger's and Peters' anomalies.

In their study of exfoliative glaucoma they point out that its hereditary pattern cannot be assessed in a simple manner. The 2 factors goniodysgenesis and exfoliation are genetically separate. Goniodysgenesis is thought to be dominant, whereas the hereditary pattern of exfoliation is still unknown. In patients with exfoliative glaucoma the authors describe a membrane blanketing the angles stretching from the iris root and passing up to the line of Schwalbe. In many cases there is a pronounced dehiscence at the 6 o'clock position, where there is an accumulation of pigment. Within the coloboma the true recess of the angle with the scleral spur is visible and at times the anterior rim of the ciliary band. It seems likely that the main stream of aqueous is trained through this port, so that the filtering pores of the outflow channels become increasingly clogged to produce at first a slow elevation of intraocular pressure. Sooner or later this moderate rise is abruptly changed into severe hypertension. Inevitably exfoliative glaucoma becomes a surgical problem.

In their study of pigmentary glaucoma they point out that pigmentary blocking of the pores cannot be the only factor, since the full pigmentary dispersion syndrome is encountered in many eyes without glaucoma. The authors introduce the dysgenetic sign into the picture of pigmentary glaucoma and agree with Malbran, who found in nearly all cases of pigmentary glaucoma gonioscopic evidence of a maldeveloped angle with anterior insertion of the iris. He concluded that pigmentary glaucoma may be classified as a true congenital glaucoma with a blanketing of the uveal meshwork corresponding to the membrane of Barkan. The hereditary pattern of pigmentary glaucoma is bifactorial and similar to that of exfoliation glaucoma.

In the chapter on simple chronic open-angle glaucoma the authors infer that this classification is an anachronism. In their series simple glaucoma is diagnosed by a process of exclusion and accounts for only 5% of all cases. The largest percentage is congenital (55·6%), followed closely by exfoliation glaucoma (35·6%). Pigmentary glaucoma accounts for 1·2% and closed-angle glaucoma 1·7%. After their clear exposition of the importance of goniodysgenesis in most types of glaucoma the authors put forward the idea that goniodysgenesis is the real cause of simple glaucoma but the signs may be so minimal as to be difficult to diagnose with the gonioscope.

The proceed to discuss goniodysgenesis and closed-angle glaucoma, particularly of the chronic type, and make a strong case for maldevelopment of the angle as a factor in this type of glaucoma as well as in cases of glaucomato-cyclitic crises. They also suggest that the corticosteroid response is one which is probably secondary to goniodysgenesis.

The final chapter is on therapeutic considerations. Following the introduction of trabeculectomy, which is a relatively safe surgical procedure, they are of the opinion that it is unwise to withhold trabeculectomy in favour of doubtful medical control, particularly as trabeculectomy is a surgical exercise attacking the main aetiological factor in glaucoma (goniodysgenesis) by excising a section of abnormal trabecular and pretrabecular tissue, allowing flow of aqueous into the region of the canal of Schlemm.

J. B. S. Haldane states somewhere in his writings that in his opinion 'the salt of the earth' are 'those who work and think about their work'. There is no doubt that the authors of this short book on goniodysgenesis, with the subtitle 'A new perspective on glaucoma', qualify for this description. They have lived with their patients and studied them with extraordinary care. Their thesis is thought-provoking and an expression of years of devoted attention to detail. S. J. H. MILLER

Strichskiaskopie. By WOLFGANG GRIMM, CHRISTIAN UCKE, and DIETER FRIEDBURG. Pp. 93. DM33. Ferdinand Enke Verlag: Stuttgart. 1978.

Streak retinoscopy is regarded by most ophthalmologists as an art rather than a science. This comprehensive volume discusses the optics and practice of retinoscopy and includes a large number of ray diagrams and experiments with artificial eyes. Many ophthalmologists will find the information about this relatively simple technique too detailed, but the book should appeal to opticians and those studying optics. T. J. FFYTCHE

Obituary

Robert Leishman, MD, FRCP Glas, DOMS

Dr Robert Leishman, a distinguished eye surgeon, died on 1 May 1979. In active practice until his retirement in 1975, he had been consultant ophthalmologist in the Victoria Infirmary and Southern General Hospital in Glasgow and honorary clinical lecturer in the University of Glasgow, and made an international reputation following his research and publication on vascular disease in the eye and other topics.

Robert Leishman was born on 31 March 1910 and was educated at Stirling High School and the University of Glasgow, where he was an outstanding student, graduating MB, ChB in 1932. After a period as house surgeon in Glasgow Royal Infirmary he practised in London until the outbreak of war, gaining experience in the specialities of ophthalmology and otolaryngology until he volunteered for duty and served as surgeon lieutenant commander RNVR with the Royal Navy and Royal Marine Commandos in several theatres of war. He was glad to have been in active service, but with his natural talent for research he was recalled to the Government Research Department at Porton, where he worked on defence against biological warfare. During this period he was influenced by Ida Mann, Foster Moore, and others, who stimulated his wish to enter the specialty of ophthalmology, and he was appointed an ophthalmologist to the Royal Navy serving in London until his return to civilian life in 1946.

He left the Royal Naval Establishment in Queen Anne's Mansions in London in 1946 to join the staff of the Tennent Institute in the University of Glasgow under the late Professor W. J. B. Riddell. From then until his retirement in 1975 he enjoyed a full career in ophthalmic surgery. He carried out research (graduating MD with honours in 1948) and lectured extensively, not only in the medical school but to innumerable professional bodies and lay organisations. In addition to his hospital work in Glasgow Western Infirmary and the Royal Hospital for Sick Children he built up a successful private practice based on his clinical ability and his excellence as a surgeon, supported by his sympathy for patients with eye disease and his understanding of their problems. Most of his patients regarded him as their friend and many became close friends.

Dr Leishman left the Tennent Institute in 1953 to become senior consultant ophthalmologist in the Victoria Infirmary and Southern General Hospital, Glasgow, where he remained until his retirement. He built up an excellent eye department in the Southern General Hospital, attracting staff from this country and overseas, and was a good and popular teacher of students, but he will be remembered principally for his research in many fields of ophthalmology and particularly for his carefully reasoned work on the effects of vascular disease on the eye, which brought him the Treacher Collins prize in 1954. With subsequent international recognition he became an authority on this subject.

Robert Leishman had many interests in addition to his profession, and he enjoyed all aspects of life. He devoted himself to his patients and research, and although his name was a byword among his ophthalmic colleagues and physicians he rarely attended meetings and was amazed by the trend he saw in his later years towards national, international, and world congresses, 'teach-ins', and television interviews, believing, as so many do, that more is achieved in the intimacy of consultation or in quiet reading and research than by these modern phenomena. He is survived by Mrs Leishman and by their son, Ralph.

Notes

Intraocular Implant Society

The United Kingdom Intraocular Implant Society will hold its next workshop at the Birmingham and Midland Eye Hospital on 15–16 November 1979. Details from Mr J. L. Pearce, Hon. Secretary, 2 Windsor Street, Bromsgrove B60 2BG.

Contact lens practice

An advanced course in contact lens practice will be held on 19–23 November for medical practitioners, limited to 25 delegates. The lectures and topics discussed will be at symposium level and will be held in the Contact Lens Department at Moorfields Eye Hospital, London. Applications to join the course should go to the Dean, Institute of Ophthalmology, University of London, Cayton Street, London, EC1. Successful applicants will be notified of the cost of the course.

Intraocular lens implants

The Florida Ophthalmological Society will hold a 4-day symposium on 'Complications of intraocular lens implants', at the Boca Raton Hotel and Country Club, Boca Raton, Florida, on 6–9 December 1979. Further information may be had from Thomas R. Bates, MD, 85 W Miller Street, Orlando, Florida 32806, USA.

Contact lens research

The International Society for Contact Lens Research has recently been established as a completely independent body which will meet periodically and transactions will be published. Membership is by election and all must be bona-fide research workers in contact lens practice. The Corresponding Secretary is Raymond I. Myers, OD, University Club Tower, 1034 S. Brentwood, St Louis, MOD 63117, USA. The Chairman of the Steering Committee is Montague Ruben, FRCS, 5 Devonshire Place, London W1.

Ocular fine structure

The European Club for Ocular Fine Structure will hold its next meeting in West Berlin in April 1980. The club was formed in 1972 to bring together annually young electron microscopists actively engaged in the study of problems relevant to the subject of ophthalmology. Further details may be had from the Organising Secretary, Dr J. P. Harnisch, Klinikum Steglitz, Augenklinik, Hindenburgdamm 35, West Berlin, West Germany.

Change in style of references

In accordance with the Vancouver agreement many medical journals are to standardise the instructions they issue to authors on the preparation of articles. References will be cited by the numerical system already familiar in many journals, including the *British Medical Journal*.

A paper (or book) cited in the text is referred to there by a superscript number. In the list of references the papers (or books) appear in the numerical order in which they are first cited in the text, not in alphabetical order by authors' names. For convenience in preparing the typescript the reference number may be typed between parentheses on the line, not superscript. The titles of journals will be abbreviated in accordance with the style of *Index Medicus*. In the typescript they should either be abbreviated in that style or given in full. This journal will change to the numerical system from the first issue of 1980. *Authors submitting papers are asked to adopt it now in order to facilitate editing*. Three examples follow:

1 Green A B, Brown C D, Grey E F. A new method of measuring the blood glucose. *Br J Ophthalmol* 1980; 64:27–32.

2 Green A B, Brown C D. *Textbook of Medicine*. London: Silver Books, 1980.

3 Grey E F. Diseases of the pancreas. In: Green A B, Brown C D, eds. *Textbook of Medicine*. London: Silver Books, 1980; 349–362.

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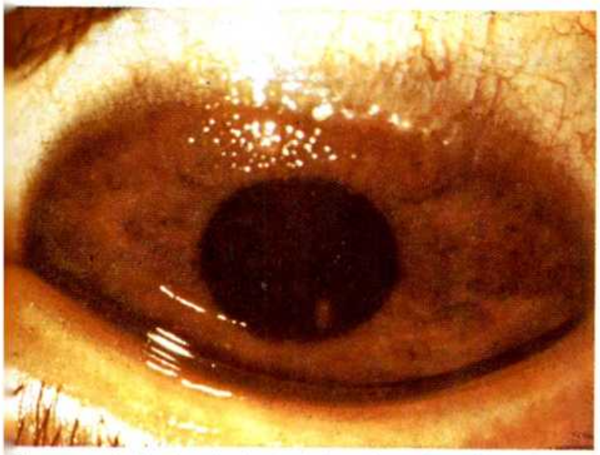
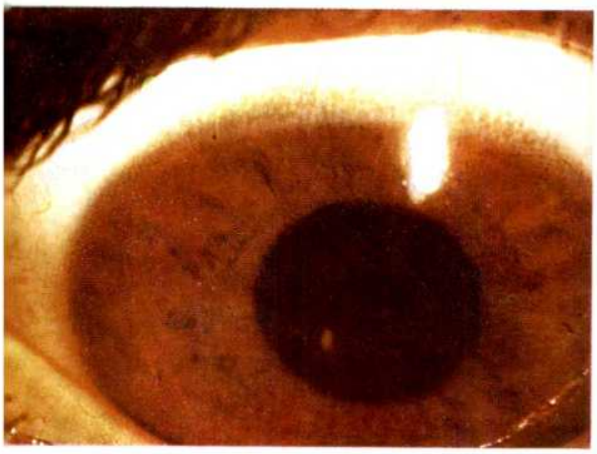
n his eyes, allergy is much more than a minor irritation.



The superior limbus in a placebo treated eye of a patient suffering from nal kerato-conjunctivitis, stained with fluorescein. Note the limbal peraemia and swelling and the irregularity of the corneal surface.



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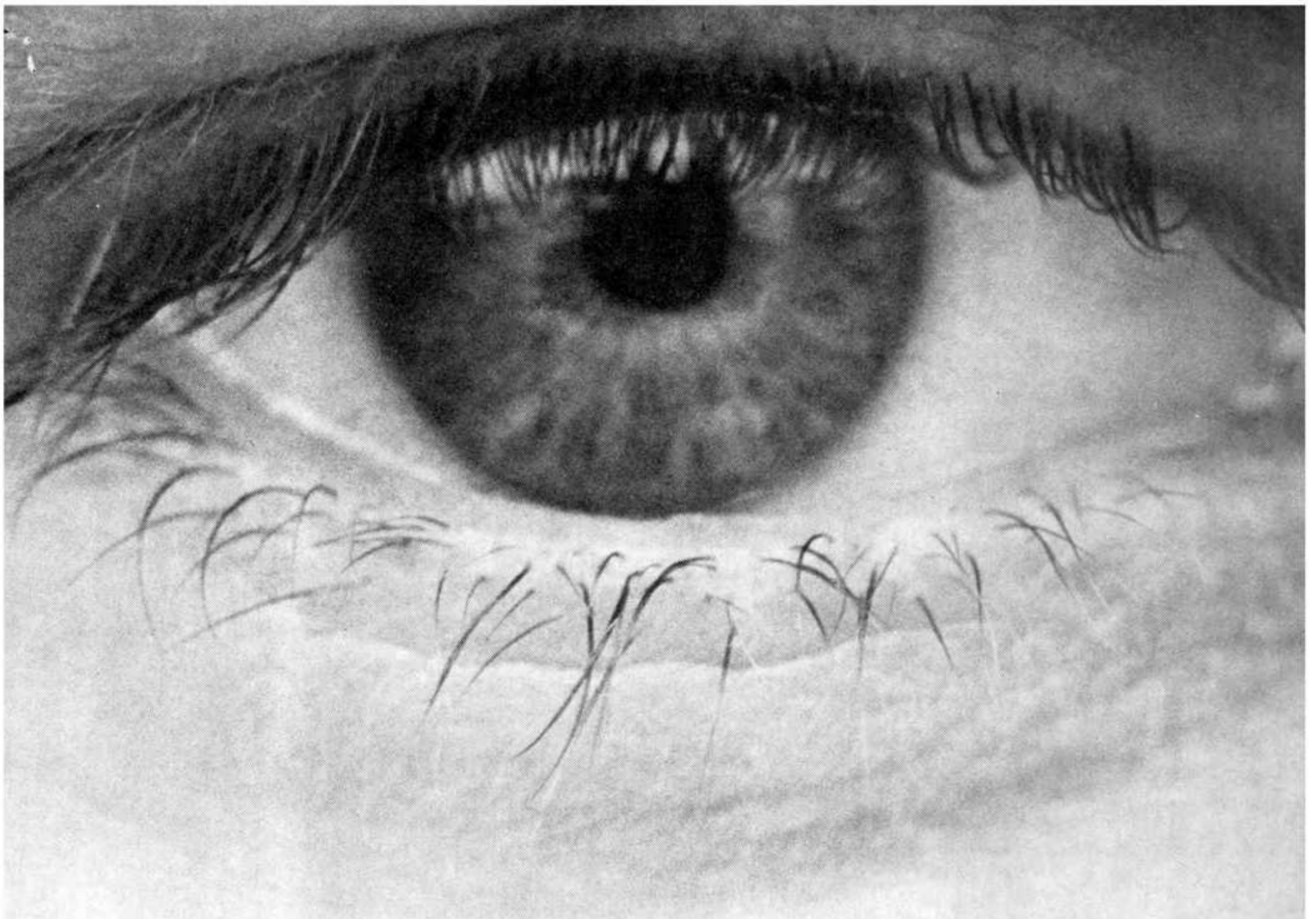

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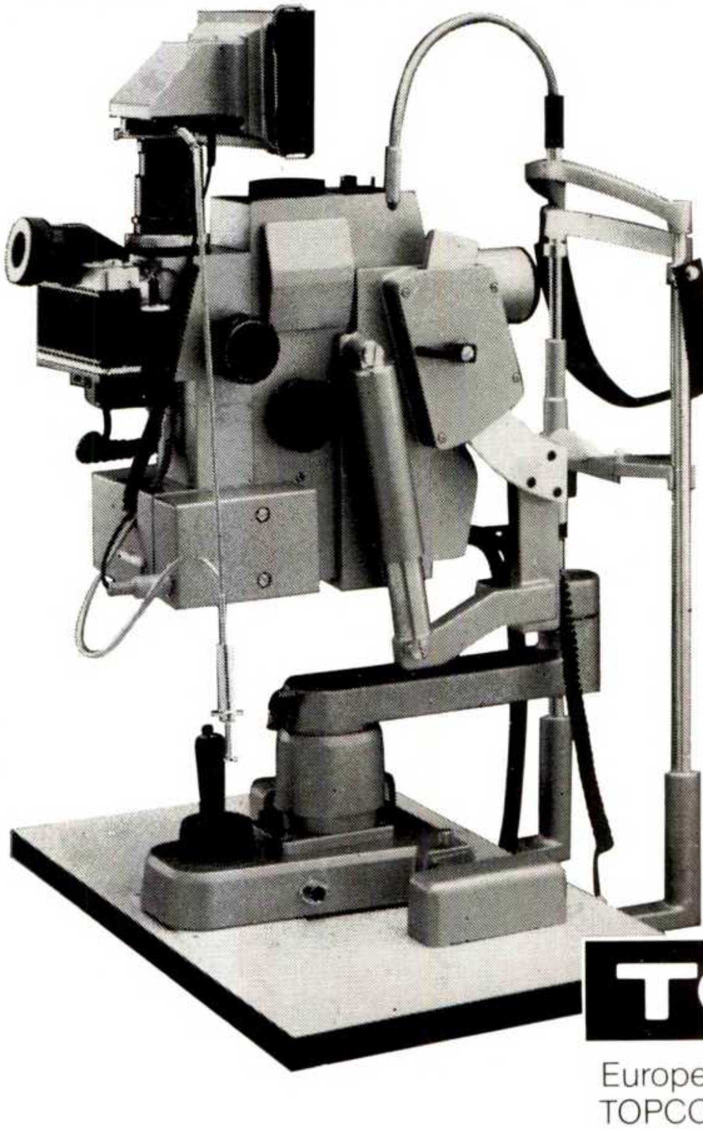

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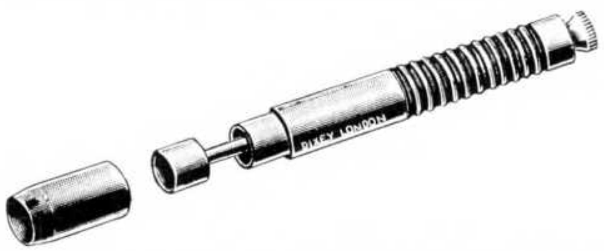

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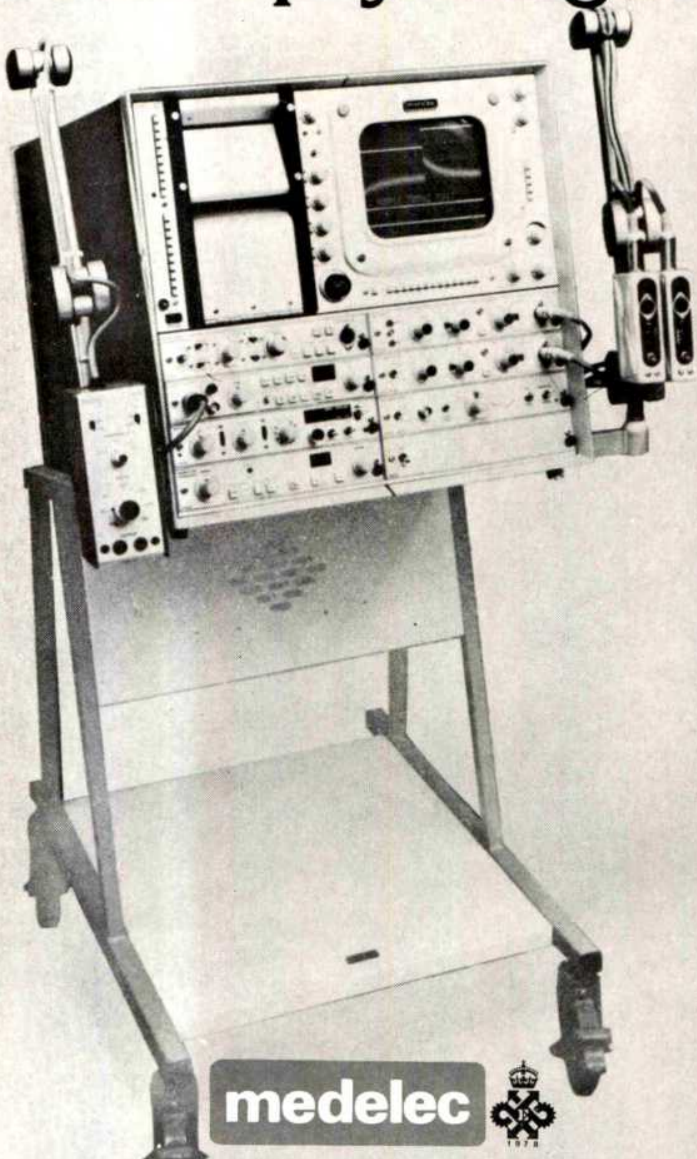

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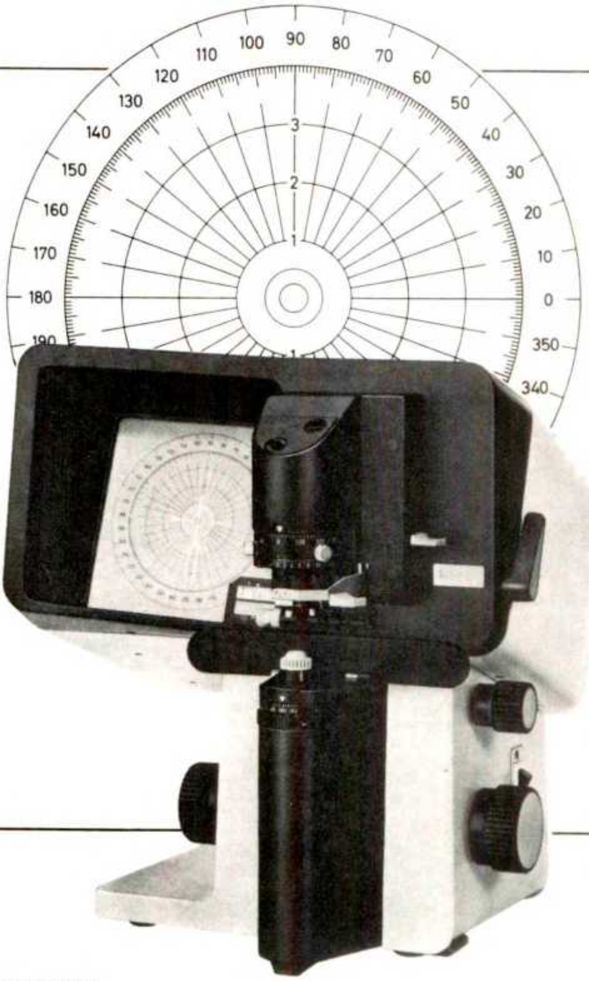

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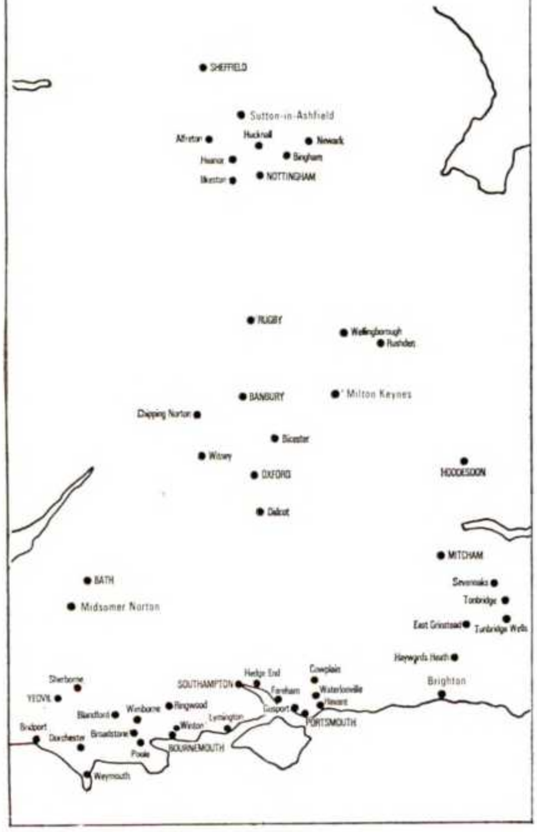

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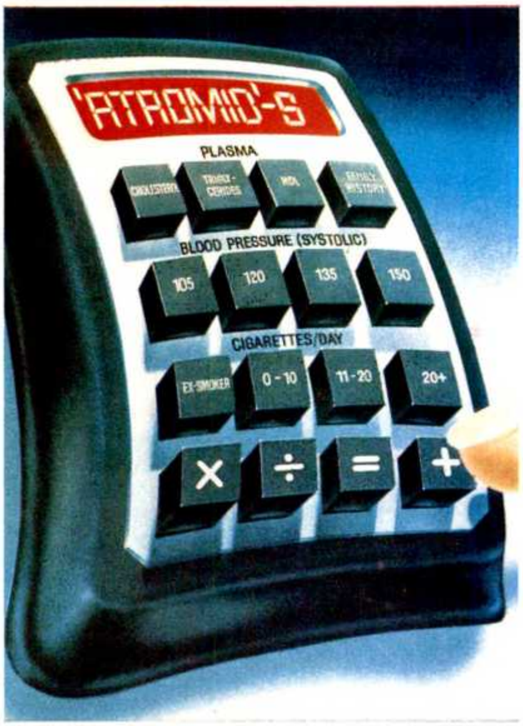

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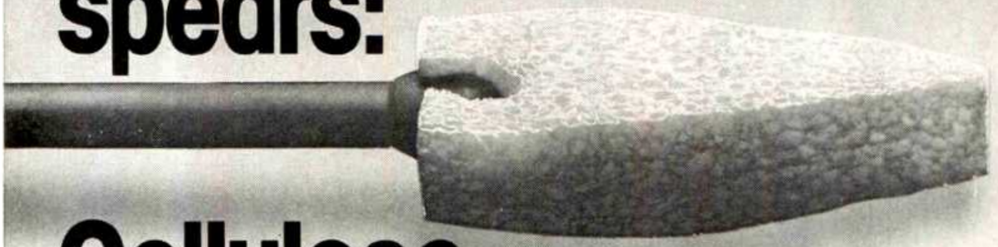

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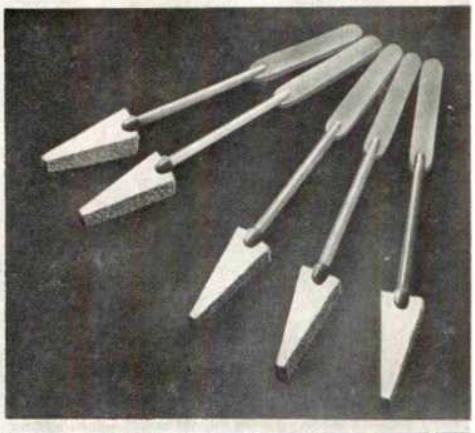

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PROGRAMME

Sunday, March 9: INTERNATIONAL GLAUCOMA CONGRESS, Session I. Faculty: Drs. David G. Campbell, U.S.A.; Raymond Etienne, France; H. Fanta, Austria; S. Fyodorov, U.S.S.R.; Richard W. Green, U.S.A.; K. Iwata, Japan; Paul L. Kaufman, U.S.A.; C. E. T. Krakau, Sweden; Mikhail M. Krasnov, U.S.S.R.; Marvin, L. Kwitko, Canada; Maurice E. Langham, U.S.A.; Adolphe A. Neetens, Belgium; A. P. Nesterov, U.S.S.R.; Harry A. Quigley, U.S.A.; Alan L. Robin, U.S.A.; Katsuzo Segawa, Japan; E. van Beuningen, Germany; Pal Weinstein, Hungary; Jacob T. Wilensky, U.S.A.; Thom J. Zimmerman, U.S.A.

Monday, March 10: INTERNATIONAL GLAUCOMA CONGRESS, Session II. Faculty: Drs. Robert K. Abraham, U.S.A.; O. P. Benedikt, Austria; Michael Blumenthal, Israel; Bruno Boles-Carenini, Italy; M. G. Bucci, Italy; Edward Grom, Venezuela; Enrique Gutierrez, Venezuela; Ryozo Kimura, Japan; Edoardo Maselli, Italy; Irvin P. Pollack, U.S.A.; Svatopluk Rehak, Czechoslovakia; Ralph S. Sando, U.S.A.; Gerald Stiegler, Switzerland; Uriel Ticho, Israel; Zarko M. Vucicevic, U.S.A.; R. Witmer, Switzerland.

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Wednesday, March 12: **STRABISMUS/PEDIATRIC OPHTHALMOLOGY SEMINAR.**
Chairman: Donelson R. Manley, MD, Wills Eye Hospital, Philadelphia, PA.

Thursday, March 13: **CORNEA AND EXTERNAL DISEASES SEMINAR.**
Chairman: Claes H. Dohlman, MD, Professor and Chairman, Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary.

Friday, March 14: **CONTACT LENS SEMINAR.**
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Saturday, March 15: **OCULOPLASTIC SURGERY SEMINAR.**
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British Journal of Ophthalmology, 1979, **63**, 655–656

Editorial: Search for the ideal laser

Since photocoagulation was first described as a method for inducing chorioretinal adhesions around retinal holes (Meyer-Schwickerath, 1949), there has been a remarkable increase in its use in the treatment of many and varied fundus disorders.

Soon after the advent of lasers (Maiman, 1960) potential advantages were identified for these sources of energy over xenon in the creation of therapeutic coagulation. The original lasers were based on crystals of ruby (chromium in corundum) and emitted short (millisecond) bursts of monochromatic collimated light. Its monochromaticity reduced optical aberrations in the focusing systems, and its coherence and therefore collimation gave such high energy density that thermal coagulation could be achieved in a small area with very short pulses (Kapany *et al.*, 1963). Thus the destructive lesions could be placed more accurately and movement of the patient's eye became less of a problem. It was also thought that the compact nature of the original ruby laser clearly made it a more useful clinical tool than the bulky xenon photocoagulators available at that time.

The ruby laser had its adherents (Beetham *et al.*, 1970), but in recent years the argon laser has become more popular and has almost totally displaced its predecessor. The major advantage claimed for argon laser energy was its wavelength (488 and 514·5 nm), which allowed direct coagulation of retinal blood vessels, since a large proportion of its energy was absorbed by blood. This was deemed valuable, since it would allow direct closure of forward growing blood vessels, which represent the major blinding complication of diabetes and retinal venous occlusion. This laser differed from ruby in that it emitted light continuously. Most practitioners preferred the longer time pulse available from the CW laser, since the lesions produced appeared to be more constant and explosions seemed less common. Interestingly, the use of the longer pulse negated one of the advantages originally claimed for the laser, since reflex eye movements can occur during pulses of 200 ms or more, and some practitioners have reverted to using retrobulbar anaesthesia. It is likely that one of the major reasons for the popularity of argon lasers was the accurate slit-lamp delivery system provided with commercially available models.

It is now evident that direct coagulation of retinal blood vessels has been largely abandoned in the treatment of retinal vascular disease with forward growing blood vessels, and panretinal ablation has become the standard therapy. Therefore it is justifiable to re-examine the rationale for using argon laser as the main energy source for photocoagulation, since it is now evident that no particular advantage accrues from its wavelengths.

The concept of peripheral ablation for diabetic retinopathy arose from the observation that diabetic retinopathy did not occur or was mild in eyes with disseminated chorioretinal scars. This was undertaken originally by diathermy (Amalric and Azema, 1963) and subsequently by photocoagulation (Beetham *et al.*, 1968). Though the mechanisms by which photocoagulation influence diabetic retinopathy are undefined, it has been amply demonstrated that inducing outer retinal damage causes reversal of certain sight threatening complications of retinal vascular disease (Diabetic Retinopathy Study Group, 1976; Cheng *et al.*, 1977). To create such lesions the primary site of energy absorption is the retinal pigment epithelium; the absorption spectrum of retinal pigment epithelium indicates that argon energy is well absorbed by this chromatophore, but many other wavelengths would also be suitable to cause outer retinal damage (Gabel *et al.*, 1977).

In the treatment of retinal vascular lesions other than retinitis proliferans it is likely that the main therapeutic effect is related to energy absorption in the pigment epithelium. Proliferation of subretinal vascular tissue within disciform macular lesions represents another major ocular disorder in which photocoagulation has been used. It is possible that some absorption by the abnormal blood vessels occurs and that obliteration may contribute to this. However, the pigment epithelium is in close proximity to the tissue, and this represents an alternative absorption site by which photocoagulation may destroy disciform lesions.

Two major disadvantages have been identified for argon wavelengths. Firstly, the energy is absorbed within the inner retina at the fovea, and it has been assumed that this absorption is by the luteal pigment (Marshall *et al.*, 1974, 1975). This phenomenon may represent a limiting factor in the treatment of disciform macular lesions, since it will prevent irradiation of parafoveolar, subretinal, neovascular complexes and reduces the percentage of lesions amenable to therapy. Secondly, the absorption by retinal blood vessels may result in macular infarction during the treatment of disciform lesions, and accidental coagulation of blood vessels may also occur during panretinal ablation for diabetic retinopathy.

The only alternative continuous wave laser at present commercially available with a slit-lamp delivery system is the krypton laser (641 nm). In theory the radiation from this laser should pass through both blood vessels and parafoveolar retina without significant absorption or damage being produced in the tissue. The characteristics of krypton laser lesions in the human fundus have been examined and the results are published in this issue by Marshall and Bird. The theoretical predictions concerning the pattern of damage have been proved correct and the potential advantages of krypton over argon demonstrated. Subretinal structures may be coagulated at the foveola without any secondary lesion appearing in the inner neuroretina, which may allow a higher percentage of disciform lesions to be treated than is the case at present with argon. Similarly, lack of absorption by blood avoids the risk of accidental retinal blood vessel closure. A possible disadvantage of krypton may be excessive absorption of radiation within the choroid since calculations suggest that up to 85% of the energy incident on the pigment epithelium can pass into the choroid (Gabel *et al.*, 1977). Choroidal vascular changes have been observed in experimental lesions in man, as Marshall and Bird note.

Preliminary clinical experience with krypton shows that this source of energy may represent an alternative to argon (Schulenberg *et al.*, 1979; and see paper by Bird and Grey in this issue). However, choroidal haemorrhages were identified during peripheral ablation for diabetic retinopathy, krypton laser energy gave rise to more pain than argon, and peripheral choroidal oedema was more common with krypton than argon. It is likely that these phenomena can be related to high transmission of energy to the choroid.

Nevertheless, each laser appeared to be as effective as the other in inducing forward blood vessel closure, and the lack of blood vessel absorption simplified coagulation around the optic disc. It is possible that adequate ablation could be achieved with krypton in a patient in whom a small amount of blood in the vitreous would prevent treatment by argon. It has also been shown that disciform lesions may be treated successfully with krypton laser energy, and the potential advantages of krypton over argon were evident to Bird and Grey, though no definite conclusions concerning the relative therapeutic merits of the two lasers could be drawn for such a small series of patients.

It is likely that the ideal therapeutic laser is not commercially available. Such a laser would produce energy at a variety of wavelengths, so that it would be possible to select a particular wavelength for each specific treatment protocol. A compromise may be a laser producing a single wavelength absorbed well by pigment epithelium but poorly by blood and by luteal pigment; such a laser would have a wavelength shorter than krypton but longer than argon. The proof that such a laser had significant therapeutic benefits over those now available would depend on controlled clinical trials, but it is justifiable to explore the possibility of its production.

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British Journal of Ophthalmology, 1979, **63**, 657–668

A comparative histopathological study of argon and krypton laser irradiations of the human retina

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SUMMARY A series of comparative exposures to both argon and krypton lasers have been made at 3 locations in a human retina—the fovea, the macula, and intraretinal vessels. In the fovea argon irradiations resulted in damage to both the inner and outer retinal layers as a result of absorption within the pigment epithelium and the macular pigment, while krypton exposures damaged the outer retina and the choroid. In the macula both systems resulted in damage to the outer retina, and again sufficient krypton radiation passed into the choroid to induce blood vessel occlusion, haemorrhage, and oedema. When intraretinal vessels were irradiated, only with argon was sufficient energy absorbed within the vessels to damage them or their surroundings in the inner retina. The implications of these findings are discussed in relation to the therapeutic uses of lasers.

Both the initial destruction and the secondary tissue responses induced by the coagulative action of laser radiation on retinal tissue are exploited therapeutically in ophthalmology. The primary reaction in most clinical exposures is one of tissue destruction resulting from the forces generated by the thermal degradation of the incident energy absorbed in the target tissue (Marshall, 1970). The amount of energy absorbed is a function of the wavelength of the incident radiation and the absorption characteristics of the irradiated media. The degree and extent of destruction within a tissue are also related to the magnitude of the exposure energy, the area of irradiation, and the duration of the exposure. Throughout the visible spectrum the predominant absorption site in the retina is the pigment epithelium, and the physical parameters of most clinical exposures are such that only this layer and the overlying photoreceptor cells are damaged. In the 1960s such a burn configuration with damage confined to the outer retina was not considered useful for the treatment of many neovascular conditions, especially those in which forward new vessels occurred. At that time the ideal system was considered to be one with which vessels could be directly irradiated by a source with a wavelength which would be absorbed by haemoglobin. The argon laser met such requirements (L'Esperance, 1968), and for some time various protocols for direct irradiation of neovascular systems were developed (Little *et al.*, 1970). Such techniques continue to be used in the treatment of subretinal neovascular complexes or disciform lesions (Gass, 1971, 1973; Bird, 1974).

Direct treatment of new blood vessels in diabetes (Little, 1973) has been largely replaced by peripheral ablation, whereby large areas of the outer retinal layers in the peripheral fundus are destroyed (L'Esperance, 1975a). Furthermore, in disciform lesions at least part of the new vessels are close to the pigment epithelium, and therefore, irradiation energy absorbed within this layer may be responsible for blood vessel closure. Thus, at present, treatment regimens for both these neovascular lesions are utilising the pigment epithelium as the absorption site and are not dependent upon the blue-green (488, 514·5 nm) emission of the argon laser. In some circumstances there is evidence that the use of these wavelengths may be counterproductive, resulting in undesirable complications. For example, when treating disciform lesions close to the fovea approximately 70% of the incident energy at 488 nm will be absorbed by macular pigment and may result in nontherapeutic destruction in the inner retinal layers and prevent irradiation of the target tissue (Marshall *et al.*, 1974, 1975). Further, when argon irradiation falls upon intraretinal vascular elements, unnecessary damage may be induced in adjacent neurones (McLeod *et al.*, 1977). For these reasons it may be desirable to use lasers that emit

Correspondence to Professor Bird.

red light. Historically such lasers have not been favourably received by ophthalmologists, but the problems with these early lasers have now been shown to be unrelated to wavelength and to have resulted from instrument design. The poor results obtained with the ruby lasers (694·3 nm) may have been due to short pulse duration of these devices, and the limited experiments with helium neon (632·8 nm) failed mainly because of inefficient optics in the delivery systems (Manson *et al.*, 1972). There are now commercial systems available that enable either argon (488 nm) or krypton (641 nm) radiation to be used for the treatment of retinal disease. Thus for the first time the relative merits of red and green light may be assessed by using continuous wave lasers with similar optical systems.

The present paper describes the histopathology of both argon and krypton irradiations in a variety of locations on the fundus and relates their morphology to the physical parameters of the irradiating sources.

Methods and materials

Two different laser systems were used in the present study, a Coherent Radiation 800 argon laser, and a Lasertek krypton laser. Although the Lasertek system may be used to deliver either krypton or argon radiation we thought that the use of the Coherent Radiation argon system would allow a more useful comparison as this model has been widely adopted in clinical centres. Both of these lasers have integral power monitors and all figures quoted are those registered on the manufacturers' instruments. No study was undertaken of the relative energy distribution within the laser beams.

Exposures were delivered via the integral slit-lamp systems in conjunction with a Goldmann fundus contact lens. One eye of a single patient was exposed 20 hours prior to enucleation for a malignant melanoma of the anterior choroid; the retinal detachment in this patient did not involve the posterior pole.

In a peripheral area of retina trial exposures were undertaken in order to adjust power levels so that approximately equal tissue responses were achieved. These exposures showed that for any given image size and exposure time krypton exposures always required higher power levels to achieve an equiretinal response to that of argon.

Two groups of 0·2 to 0·5 second exposures were made with each type of laser. In the macula a series of 8 argon exposures were made in a line on the superonasal to inferotemporal axis and which traversed the fovea (50 μm image size, 87 mW). A similar number of krypton exposures were made at similar distances from the fovea at right-angles to lines of argon burns (50 μm image size, 200 mW). One 150 mW krypton exposure was made at the foveola.

The second group of exposures involved the irradiation of similar calibre arterial and venous elements of the intraretinal circulation with both argon (200 μm, 300 mW) and krypton (200 μm, 600 mW) systems.

The eye was enucleated and processed for both light and electron microscopy as previously described (Marshall *et al.*, 1975).

Results

Ophthalmoscopic observations on the central group of argon lesions confirmed earlier findings that within 2° of the fovea the morphology of the lesions changed with a coagulation site becoming apparent in the inner retina, and that the intensity of such coagulations increased as the distance from the fovea decreased. No such inner retinal damage was observed in any of the krypton exposures (Fig. 1).

Differences were also observed between the two types of irradiation on the vascular elements. Both krypton and argon induced lesions were seen as pale white areas of coagulation at the level of the pigment epithelium. With krypton lesions the vessel and inner retina appeared unaffected clinically (Fig. 2) whereas with argon the vessel lumen was narrowed, there was haemorrhages, and opacification of the inner retina (Fig. 2). At 20 hours these

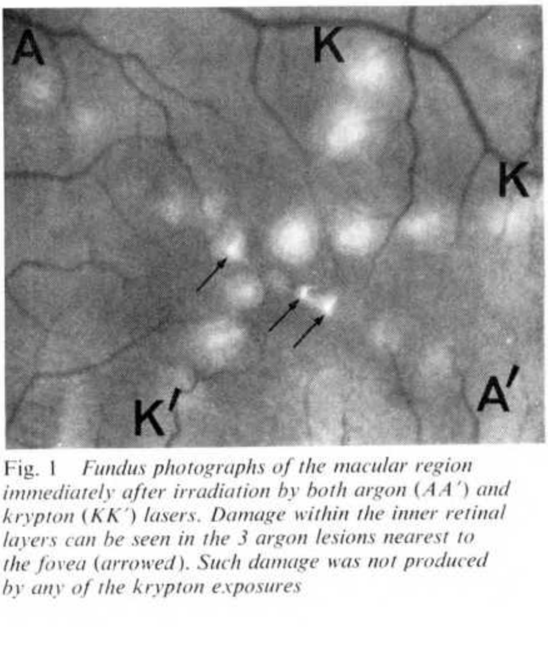

Fig. 1 *Fundus photographs of the macular region immediately after irradiation by both argon (AA') and krypton (KK') lasers. Damage within the inner retinal layers can be seen in the 3 argon lesions nearest to the fovea (arrowed). Such damage was not produced by any of the krypton exposures*

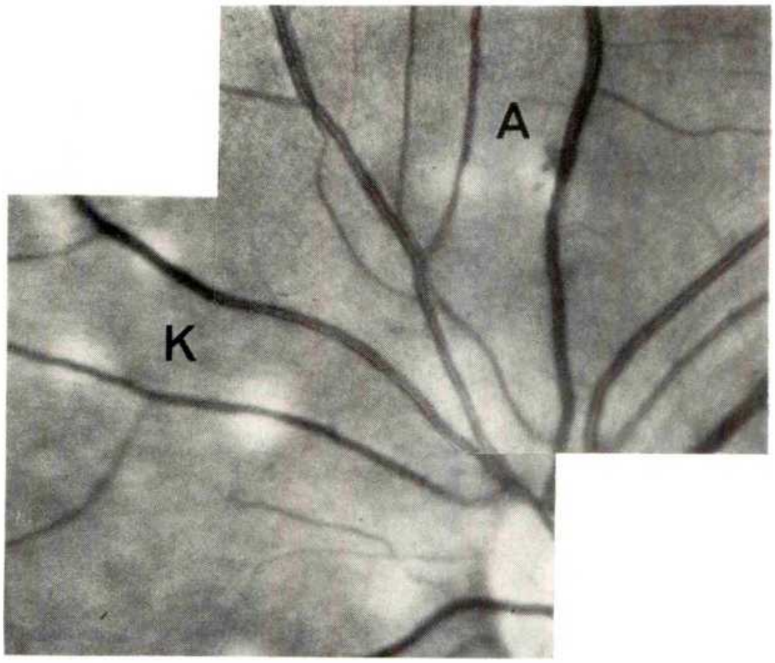

Fig. 2 *Fundus photograph of major retinal vessels immediately after irradiation by either argon (A) or krypton (K) lasers. The vessels irradiated with the argon laser characteristically show a narrowed lumen, while those exposed to krypton radiation show little effect*

argon lesions acquired an increased opacification consisting of small fluffy white crescent-shaped changes in the inner retinal layers on the side of the lesion adjacent to the optic disc.

RETINAL DAMAGE

Irradiations of the macula

All irradiations resulted in damage to the pigment epithelium and overlying photoreceptor cells throughout the area of exposure (Fig. 3).

At distances greater than 2° from the fovea argon and krypton lesions had similar morphology, except that pigment epithelial changes appeared more severe in the former. Thus in both cases the cells were either shrunken or swollen, but more extracellular space was apparent in argon induced lesions, especially in the region between the base of the cells and Bruch's membrane. In the periphery of both types of lesion the changes between irradiated and nonirradiated epithelial cells were quite marked, and cell movement had resulted in an annular zone of denuded Bruch's membrane (Fig. 3b). Some epithelial cells adjacent to irradiated areas had budded off Bruch's membrane and could be seen together with macrophages in the subretinal space between the outer segments of the photoreceptor cells (Fig. 3b, c).

The electron microscopy of subcellular changes within argon irradiated pigment epithelial cells has been previously described (Marshall *et al.*, 1975), and in the present study a similar spectrum of damage was seen in cells irradiated by krypton.

Damage to the neural retina in this region was confined to the photoreceptor cells. Both argon and krypton irradiations resulted in areas of disorganised outer and inner segments of photoreceptor cells, which were always associated with, but smaller than, the areas of pigment epithelial disturbance. Receptor nuclei in the irradiated areas were pyknotic, though in all lesions some nuclei appeared normal. Degenerative changes were also seen in the inner connecting fibres of damaged photoreceptor cells, which were abnormally densely stained where they traversed the fibre layer of Henle. No laser induced changes were observed in the inner retinal layers of any lesions in this region of retina.

Irradiations of the fovea

Irradiation within 2° of the fovea showed marked differences in damage distribution in the neural retina which were related to the irradiating wavelength (Fig. 4a).

In argon lesions in this area damage to the outer retinal layers was less severe than those seen in the outer macula. The pigment epithelial cells still showed displacement of their cell boundaries, but in equienergetic exposures the volume changes and vacuolation were less than in the more peripheral lesions. In the photoreceptor cell layer changes similar to those previously described were observed,

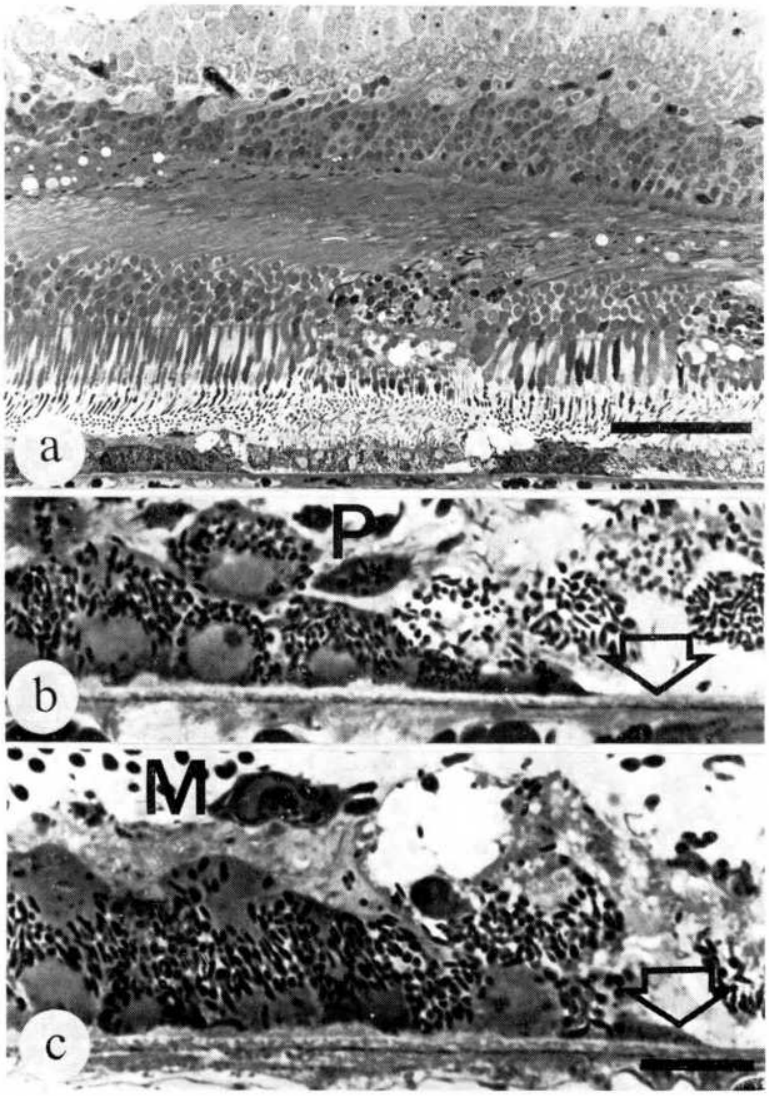

Fig. 3 (a) *Light micrograph of a krypton laser induced lesion in the macula, 20 hours after exposure. Damage is confined to the pigment epithelium and the overlying photoreceptor cells. The marker is 100 µm.* (b) (c) *Light micrographs of human pigment epithelium adjacent to krypton laser lesions (arrowed) in the macula. In* (b) *pigment epithelial cells (P) can be seen budding off Bruch's membrane, while in* (c) *a macrophage (M) can be seen in the subretinal space. The marker is 10 µm*

but again fewer cells were involved (Fig. 4b). All argon exposures resulted in gross vacuolation and tissue displacement in the inner retinal layers (Fig. 4). This second damage locus was centred on the inner nuclear layer but involved both of the plexiform layers and the ganglion cells. In all cases serial sections demonstrated that, while the inner and outer retinal damage sites were coaxial, they were discrete.

Krypton induced lesions in this region of the retina were identical to those produced in the outer macula, in that damage was confined to the outer retina, with the exception of a slightly more marked response within the pigment epithelium (Fig. 4). Thus in the fovea argon and krypton induced changes in this layer appeared quite similar.

Irradiations of intraretinal blood vessels

The larger image sizes and higher power densities used in this part of the study resulted in larger areas of damage with more severe cellular changes in the outer retina.

In the argon induced lesions changes were observed both in the irradiated vessels, and in the adjacent nerve fibres (Fig. 5). Both arterial and venous vessels showed damage or displaced endothelial cells, and a high incidence of white blood cells within the irradiated areas. Immediately

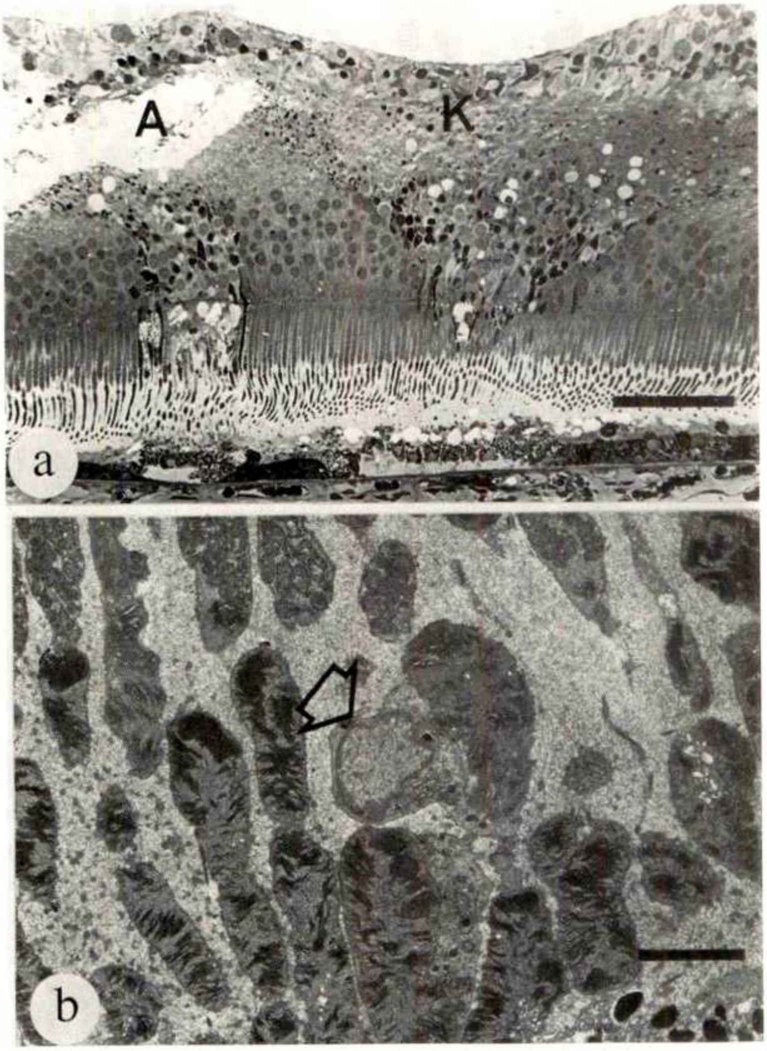

Fig. 4 (a) *Light micrograph of both an argon (A), and a krypton (K) induced laser lesion in the fovea. While both lesions show damage to the retinal pigment epithelium and overlying photoreceptor cells, only the argon induced lesion shows a discrete area of damage within the inner retina. The marker is 100 μm.* (b) *Electron micrograph of the damaged outer segments within an area of argon irradiated retina at the fovea. Within 20 hours of exposure macrophages (arrowed) can be seen engulfing these elements of damaged cells. The marker is 4 μm.*

adjacent to the basement membranes of some vessels small annular areas of vacuolation were observed, and in other lesions small haemorrhages occurred into the inner plexiform layer (Fig. 5). The most striking changes seen in association with areas of argon irradiated vessels were large spheroidal axonal swellings in the nerve fibre layer. The cross-section diameters of axons in this region of the retina were normally in the range of between 0·5 and 4 μm; however, those of the swollen portions were between 8 μm and 16 μm. These swellings, sometimes designated 'cytoid bodies', were found on both sides of blood vessels that ran parallel with the ganglion cell axons, but only on the side adjacent to the disc where vessels crossed the ganglion cell axons at right angles (Figs. 5, 6). On electron microscopy these axonal swellings were seen to contain large numbers of degenerate mitochondria, neurofilaments, and lysosomes, so densely packed that the normal axoplasm was almost excluded (Fig. 6). There were also membranous whorls and lipid bodies indicating membrane breakdown. Where vessels that ran at right-angles to the ganglion cell axons had been irradiated, less swollen but abnormally enlarged axons were also observed on the side of the vessel remote from the optic disc by electron microscopy. These swollen regions contained few organelles but had abnormal concentration of neurofilaments lining the axolemma. In all lesions some axons within the irradiated area appeared normal.

Increase in the staining density of some compo-

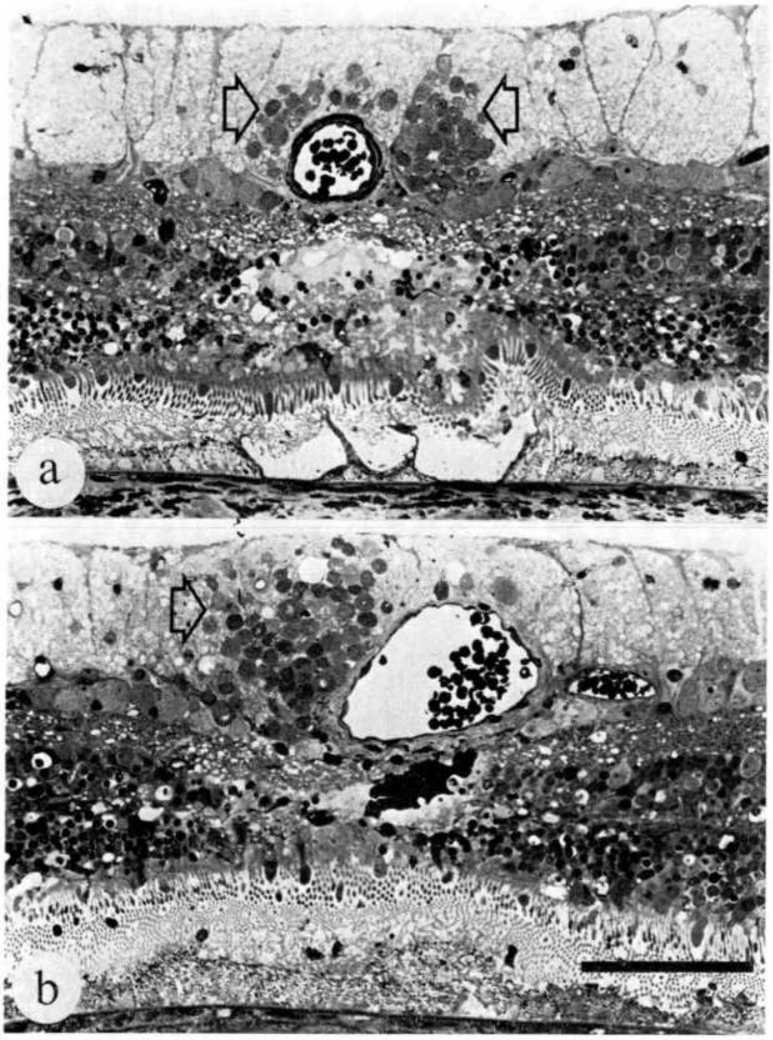

Fig. 5 *Light micrographs of* (a) *an artery and* (b) *a vein 20 hours after irradiation by an argon laser.* (a) *The nerve fibres in this region ran obliquely over the artery on their passage to the disc and hence distended nerve fibres (arrowed) can be seen surrounding the vessel. This lesion also shows a central region of less damaged pigment epithelium lying under the artery resulting from the attenuation of incident energy by absorption within the vessel.* (b) *In this lesion the nerve fibres ran more at right-angles to the vein and the hence distended axons (arrowed) are predominantly on the side nearest to the disc. This exposure resulted in a small haemorrhage into the inner nuclear layer. The marker is 100 μm*

nents of the Müller's fibres were seen, but this was largely unrelated to damage associated with intraretinal vasculature.

Damage to the neural retina induced by krypton irradiation of blood vessels was almost exclusively confined to photoreceptor cells, the exceptions being occasional densely stained Müller's fibre elements in the inner retinal layers (Fig. 7a). No damage was observed in any of the irradiated vessels, and no changes could be found in the adjacent axons of ganglion cells (Fig. 7b).

CHOROIDAL DAMAGE

In both argon and krypton irradiations there were changes in the underlying choriocapillaris adjacent to damaged pigment epithelial cells. In most lesions the capillaries were occluded throughout the irradiated areas. Blood stasis had resulted in the lumen of the vessels being either packed with degenerate blood cells or collapsed and containing remnants of endothelial cells and fibrin. Associated with these vascular changes were areas of oedema in the inner layers of the choroid. In most argon lesions damage was limited to the choriocapillaris.

By contrast vascular damage deep in the choroid was a characteristic of krypton lesion. These vascular lesions were always associated with morphological changes in adjacent choroidal melanocytes. In man these cells are usually relatively uniformly pigmented, with many branch-like processes extending from their cell bodies (Fig. 8a, b, c). Beneath areas of krypton induced damage to the retina they had lost

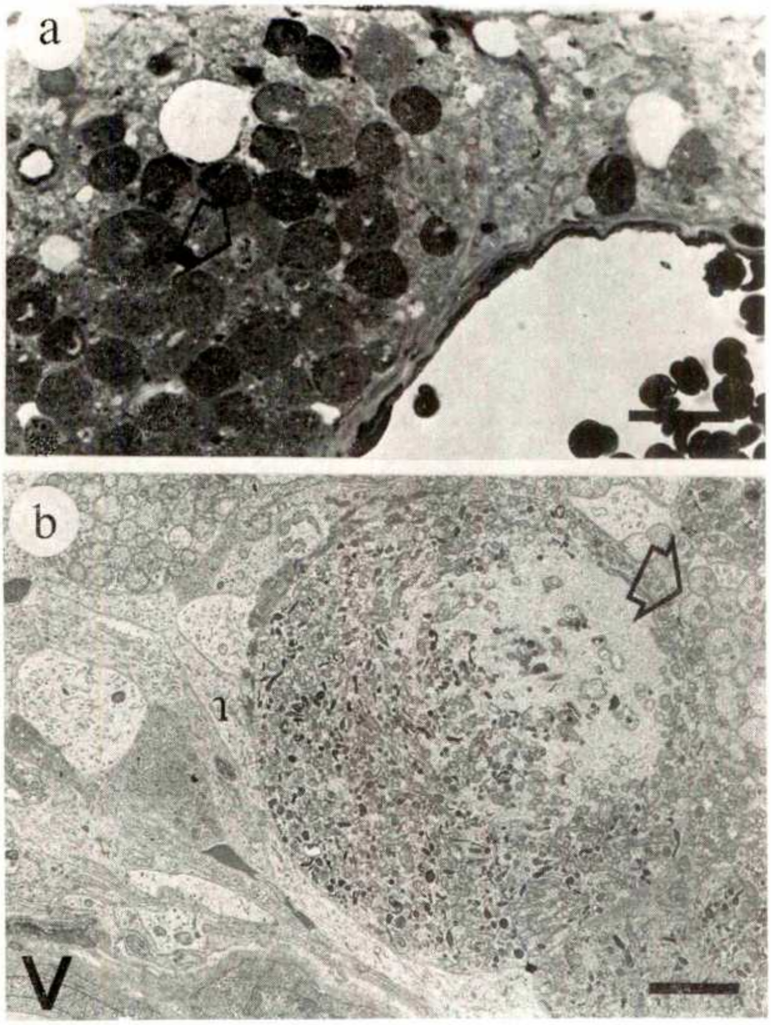

Fig. 6 (a) *Light micrograph of distended axons adjacent to an irradiated retinal vein. The pseudonuclei (arrowed) resulted in the term 'cytoid bodies' being given to these systems. The marker is 20 µm.* (b) *Electron micrograph of one such swollen axon showing that the pseudonuclei are a region filled with neurotubules, while the periphery contains many shrunken and degenerate mitochondria. Axons of normal dimensions (arrowed) can be seen adjacent to those showing damage, and (V) is the vein. The marker is 2 µm*

their lateral processes and become rounded and darkly pigmented (Fig. 8d). Macrophages were observed in the choroid associated with these damaged cells.

Three types of vascular lesions were observed, which were, in order of increasing severity, endothelial sloughing, endothelial loss with exudates, and small haemorrhages (Fig. 9). Endothelial sloughing was observed in vessels of all sizes but in large vessels was often highly focal and only in areas immediately adjacent to melanocytes (Fig. 9a). In smaller vessels, where endothelial cell loss and leakage of vessels contents had occurred small clots of platelets could be seen associated with the former areas of leakage (Fig. 9b). Exudates from many of these lesions had resulted in disorganisation of adjacent tissues.

Discussion

In any analysis of radiation induced damage to a biological system a fundamental requirement is the separation of acute radiation induced change in and adjacent to the absorption sites from the secondary tissue responses to such primary lesions. The present study involves the examination of damage produced by nonionising radiation 20 hours after exposure, and therefore much of the pattern of histological disturbance is due to tissue reorganisation in response to injury.

RETINAL ABSORPTION SITES AND PRIMARY DAMAGE

The retinal pigment epithelium is the major site of absorption of both argon and krypton radiation,

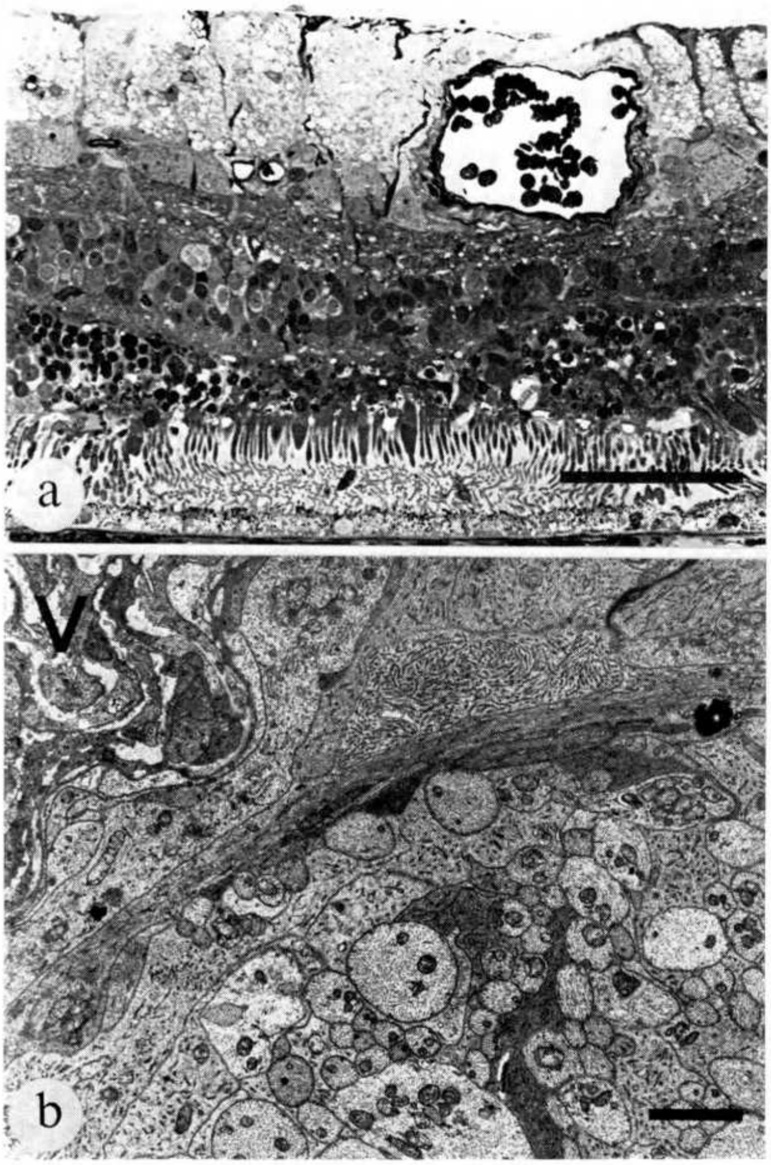

Fig. 7 (a) *Light micrograph of a vein 20 hours after irradiation by a krypton laser. In this lesion damage is confined to the outer layers of the retina and no swollen axons are observed. The marker is 100 μm.* (b) *Electron micrograph of the axons adjacent to the irradiated vein (V) shown in* (a). *The marker is 2 μm*

and in the time domain of clinical exposures all damage results from thermal processes. The most quoted studies of absorption of retinal pigment epithelium and choroid as a function of wavelengths show that, at the argon wavelength (488 nm), 73% of the incident energy will be absorbed, while only 65% of absorption will occur at that of krypton (641 nm) (Geeraets and Berry, 1968). This 15% differential in absorption between the 2 wavelengths seems inadequate to explain the factor of 2 between argon and krypton exposure energies for an equal retinal response in the macula and when exposing intraretinal vessels. However, our results indicate that in argon exposures very little energy passes through the pigment epithelium, so that in comparative studies it is the relative absorption of this layer alone that should be considered. Such measurements have been carried out by Gabel and colleagues (1977), who show that in human pigment epithelium there is a 40% differential in absorption between these 2 wavelengths and that at both wavelengths 33% less energy is absorbed in the perimacular

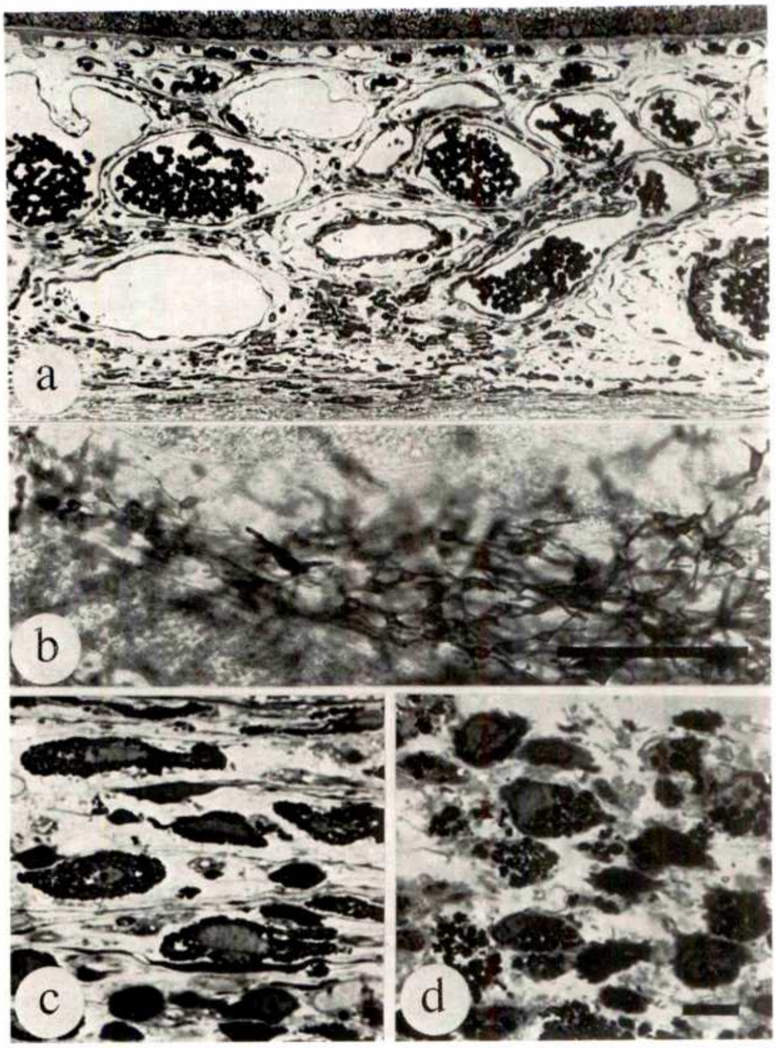

Fig. 8 (a) *Light micrograph of pigment epithelium and choroid in an unirradiated area showing the discontinuous array of choroidal melanocytes.* (b) *Light micrograph of a flat preparation of choroid showing the ameboid like processes of the choroidal melanocytes. The marker is 100 µm.* (c) *Light micrograph of unirradiated choroidal melanocytes showing their pigment distribution and the collagenous interstitial elements.* (d) *Light micrograph of krypton irradiated choroidal melanocytes showing abnormal cell profiles with pigment clumping, and the presence of both macrophages and oedema. The marker is 10 µm*

region than in the macula. Differences of this magnitude would be consistent with our observations. Further factors may have arisen due to differentials in energy distributions within the beams of the 2 systems used (Borland *et al.*, 1978). Beam energy profiles were not determined, but observations indicated that neither of the beams had a Gaussian distribution of energy.

The absorption characteristics of the macular pigment have been determined as a function of wavelength and retinal location both in vivo (Ruddock, 1963) and in vitro (Gabel and Birngruber, 1979). While the absolute absorption varies between both individuals (Bone and Sparrock, 1971; Gabel and Birngruber, 1979) and races (Ishak, 1952), the relative absorption as a function of wavelength is remarkably constant. It has been shown that between 15% and 80% of the incident energy at the argon wavelength is absorbed in this pigment but less than 1% is absorbed at that of krypton. A similar differential in relative absorption exists when haemoglobin is irradiated, where, depending on the state of oxygenation, between 10 and 50 times more light is absorbed at 488 nm than at 630 nm (L'Esperance, 1975b).

In argon exposures these intraretinal absorption systems attenuate the radiation falling upon the pigment epithelium, and therefore damage in this layer is less marked in the fovea and under retinal vessels (Bowbyes *et al.*, 1973). Very little krypton radiation is absorbed in either of these chromatophores, and only about 15% of the incident energy

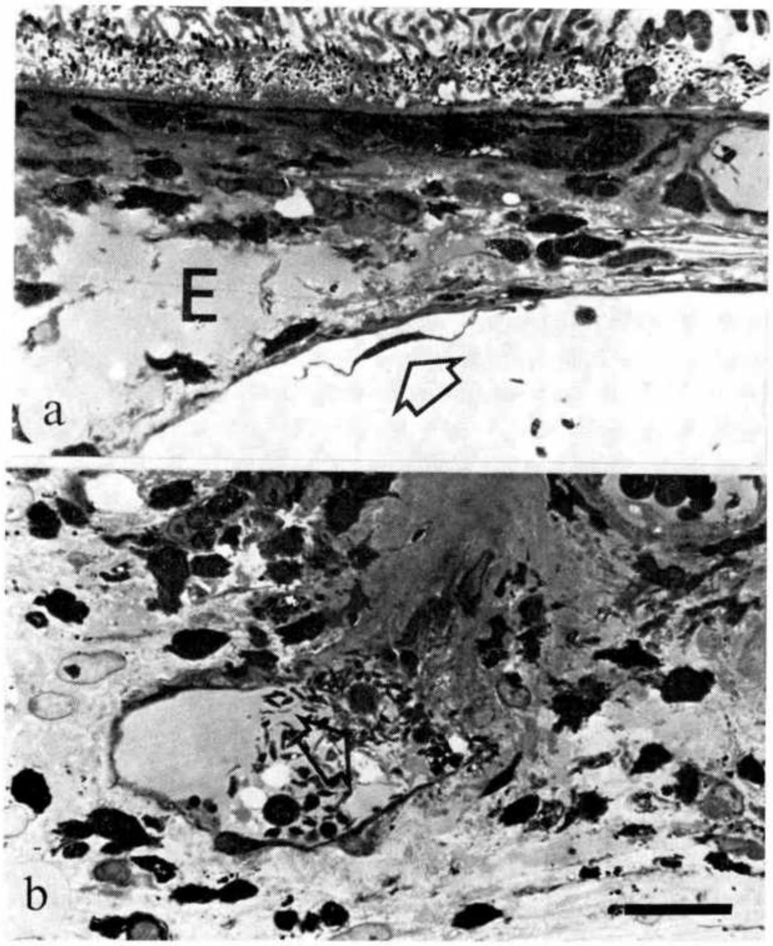

Fig. 9 (a) (b) *Light micrographs of choroidal vessels 20 hours after irradiation with a krypton laser.* (a) *A small vascular lesion showing endothelial cell sloughing (arrowed) adjacent to an area of oedema and tissue disruption (E).* (b) *A more severe vascular lesion showing clotting (arrowed) subsequent to a choroidal haemorrhage, and the presence of both oedema and denatured melanocytes in the surrounding tissue. The marker is 20 µm*

at this wavelength is dissipated within the pigment epithelium. It is therefore not surprising that in these exposures absorption within the choroidal melanocytes is of sufficient magnitude to induce damage to this layer (Figs. 8, 9).

The location of the various damage sites in the present study are clearly coincident with the sites of absorption. However, in determining the degree of damage associated with each site, not only is the relative absorption important but also the path length in which such absorption occurs. In general for any given value of absorption the shorter distance in which it occurs the greater the absorbed energy density and, above threshold, the greater the associated damage. If the thermal tolerance levels are similar for all cells throughout the retina, then damage associated with absorption by the pigment epithelium should be the most severe, as the pigment in this layer is confined to the apical 3 µm of the epithelial cells, while in most cases both macular and blood pigments are more diffusely distributed. In the present study this concept is supported by the large regions of coagulated photoreceptor cells adhering to the pigment epithelium throughout both argon and krypton irradiated areas (Figs. 3, 4, 5, 7). The extensive disturbances in the inner retinal layers in argon exposures of the macula arise through bulk tissue displacement by secondary processes of fluid leakage. Secondary processes also amplify the damage site in argon irradiation of the intraretinal vessels.

The absorption parameters of the choroid are extremely difficult to describe, as the local variations are enormous (Fig. 8). Individual choroidal melanocytes are relatively large cells, being about 80 µm in length and 10 µm in depth, and can be extremely densely pigmented. This discontinuous array of highly absorbing cells probably accounts for the focal distribution of vascular lesions seen in the krypton irradiations, where up to 85% of the energy incident on the pigment epithelium passes through into the choroid. In the present study all choroidal changes associated with argon irradiations were confined to the choriocapillaris and resulted from thermal dissipation of energy absorbed within the pigment epithelium.

SECONDARY RESPONSES TO LASER IRRADIATION

The responses of retinal cells to various types of injury are a characteristic of the cells and not the injury. Thus the differences in topographic pathology between lesions induced by lasers of different wavelengths arise through either variations in the degree of damage to individual cell types or variations in the cell types damaged. In the present study within 20 hours of exposure in both argon and krypton lesions the pigment epithelial cells immediately adjacent to the irradiated area were undergoing changes in order to contain and clear the damaged site. The rounded cells protruding into the intra receptor matrix eventually bud off Bruch's membrane and join the blood-borne macrophages in clearing the debris of coagulated cells. These wandering epithelial cells are formed either by budding from multinucleate cells (Marshall and Mellerio, 1970) or by mitotic division (Ham *et al.*, 1978), though in the present study we did not observe any mitotic figures.

The responses observed in irradiated photoreceptor cells were of degeneration and decay, and even in this short postexposure period many cells had lost large portions of their outer segments due to activity of macrophages. The degenerative changes resulting in the abnormally dense staining of the inner connecting fibres of some photoreceptor cells were shown to be extremely rapid in a previous study (Marshall *et al.*, 1975). Both the angular inclinations with respect to the axis of radiation and the length of these degenerative fibres confirm that they result from secondary degenerative processes within the cell bodies of photoreceptor cells. Primary damage resulting from intrafibre absorption was observed in the innermost part of the fibre layer of Henle in the most central argon exposures, but this damage never resulted in the complementary production of densely stained fibres radiating to remote outer portions of receptor cells. In many of these inner retinal lesions the exudates arising from adjacent damaged cells resulted in a cleavage of inner and outer retinal layers along the line of the outer plexiform layer.

The axonal swellings seen in the nerve fibre layer in areas of argon irradiation of intraretinal vessels were the most striking secondary response in the inner retina (Figs. 5, 6). Terminal swellings on either side of interrupted axons in areas of intense photocoagulation have been previously reported (Okun and Collins, 1962; Marshall and Mellerio, 1967), but it was not appreciated until recently that such swellings arise through the interruption of the bidirectional flow of axoplasmic constituents along the axon. In an autoradiographic study of both laser and ischaemic lesions in pig retina it has been demonstrated that the swelling of damaged axons occurs as a passive response to the damming of axonal flow (McLeod *et al.*, 1977). The observations in the present study are identical with those of McLeod and colleagues in that swelling due to interruption of retrograde transport in the isolated axonal segment adjacent to the optic disc was always larger than that due to orthograde flow in the segment attached to the cell body. The significance of this type of axonal damage to field loss following irradiation would be very difficult to assess, as in all lesions in this study some normal looking axons were present in the exposed areas.

The presence of oedema and macrophages in the choroid in areas of krypton irradiation is clearly a secondary response to changes in the vascular elements in this tissue, and represents an early phase of wound repair (Fig. 9).

Laser technology is now capable of producing reliable systems with a variety of emission wavelengths, and therefore there is a potential for the selective exploitation of ocular absorption sites. To do this effectively a better understanding of the particular aspects of photocoagulation which result in the beneficial changes in various types of neovascular lesions is essential. At present none of the therapeutic procedures are fully understood in terms of their reaction sequence. Thus in the successful treatment of disciform lesions we do not know whether the therapeutic response is 1° or 2° in either the new vessels, the pigment epithelium, the choroid, or some combination of these, or which tissue absorption is important in generating this change. Even more complex conceptual problems arise in optimising peripheral ablation treatment. Several authors (see L'Esperance, 1975c) have suggested that the large areas of retinal destruction result in a reduced metabolic demand and that this in turn influences neovascular atrophy. However, given the dual circulating system of the retina with a choroidal supply to the photoreceptor cells, and an intraretinal system which feeds all the inner retinal layers, it is difficult to understand how destruction of the photoreceptor cells and the underlying choroid would achieve this end in respect of the intraretinal vascular system. A further consideration is the increase in bulk fluid flow through the retinal pigment epithelium following photocoagulation, which would result in loss from the vitreous of any diffusible agent which may be influencing blood vessel behaviour (Foulds, 1976).

With this uncertainty it is impossible to predict the relative clinical values of lasers with different wavelengths with their different absorption characteristics, and different spectra of tissue damage, but as we now have the capability to damage selected regions of the retina it is hoped that future clinical studies will optimise the selection of laser wavelengths for specific retinal diseases. In particular the krypton laser allows damage to be restricted to the outer retina and choroid.

We thank Miss E. Clarke and Mr P. L. Ansell for technical assistance and Miss Julie Bramley for secretarial help. We would like to express our gratitude to Lasertek for the loan of their krypton laser. We are also indebted to the British Committee for the Prevention of Blindness, the Garrick Trust, and the Wellcome Trust for gifts of capital equipment.

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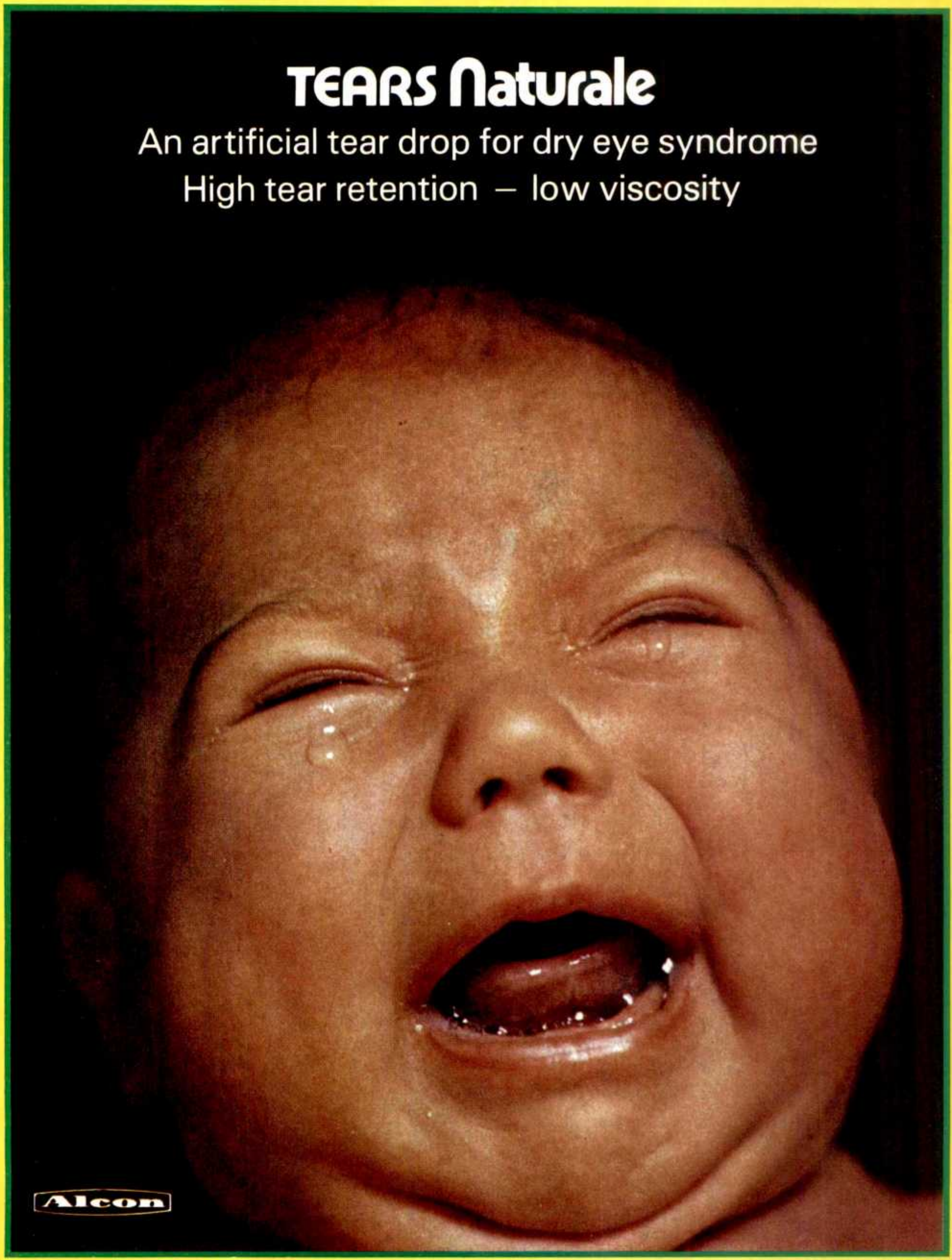

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Photocoagulation of disciform macular lesions with krypton laser

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SUMMARY Ten vascular disciform macular lesions were treated by krypton laser photocoagulation. In 8 the lesion resolved after therapy, and in 7 the retina remained flat for 6 months. On those patients treated successfully 6 had a visual acuity of 6/12 or better. The morphology of the laser lesion differed from that of the argon lesion in that there is no evidence of thermal coagulation of the inner retina near the foveola.

Successful treatment of vascular disciform lesions using photocoagulation has been documented by several authors (Gass, 1971, 1973; Schatz and Patz, 1973a; Bird, 1974), but it is clear from these reports that a significant proportion (25–50%) fail to respond to therapy. Moreover, some patients with obliteration of the subretinal neovascular tissue following treatment have poor residual visual acuity. The chances of therapeutic neovascular tissue ablation are less and the visual outcome is worse when the neovascular tissue, and therefore the required photocoagulation, is close to the foveola (Bird, 1974). Most of these observations concern the use of argon laser energy, and it has been suggested that the limitations of this form of energy may be related, at least in part, to the absorption of the green light (488 and 514·5 nm) by luteal pigment (Marshall *et al.*, 1974, 1975). Intraretinal absorption of energy will prevent delivery of energy to the subretinal tissues, may denervate the foveola, and may increase the risk of intraretinal fibrosis.

This paper reports initial experiences with the longer wavelength light of a krypton laser (641 nm) in the treatment of disciform macular lesions.

Patients and methods

Ten patients with vascular disciform lesions in which there was a discernible gap between the neovascular tissue and the foveola as shown by fluorescein angiography were selected for treatment by krypton laser photocoagulation (Table 1). Nine patients were over 60 years old and had diffuse age-related fundus disease in the eye to be treated and all but 1 (case 8) had a disciform lesion in the other. One patient was young, had presumed ocular histoplasma syndrome, and the other eye had good vision (case 10).

Table 1 *Morphological and visual outcome in patients treated with argon laser photocoagulation*

Case	*Age (yr)*	*Visual acuity* *Before treatment*	*6 months after treatment*	*Outcome*	*Proximity (microns)*	*Power (milliwatts)*
1	68	6/18	6/12	Flat	300	500
2	73	6/9	6/9	Flat	400	500
3	79	6/18	6/12	Flat	400	600
4	70	6/18	CF	DD	250	500
5	73	6/24	CF	DD	100	500
6	71	6/12	6/12	Flat	300	750
7	85	6/9	6/9	Flat	200	500
8	76	6/9	CF	DD	300	550
9	68	6/12	6/12	Flat	250	450
10	31	6/18	6/36	Flat	200	300

DD = disciform lesion at 6 months after treatment. Proximity = proximity of subretinal neovascular tissue to the foveola. Power = power in milliwatts of krypton laser beam. CF = counting fingers.

MANAGEMENT TECHNIQUE

In all patients the gap between the neovascular tissue and the foveola was measured by using a grid over the negative of the fluorescein angiogram (Gregor *et al.*, 1977). Coagulation was undertaken with Lasertek krypton laser (647 nm) with sufficient power to produce intense coagulation; a 200 μm aperture was used in each case and exposure time

Correspondence to Professor Bird.

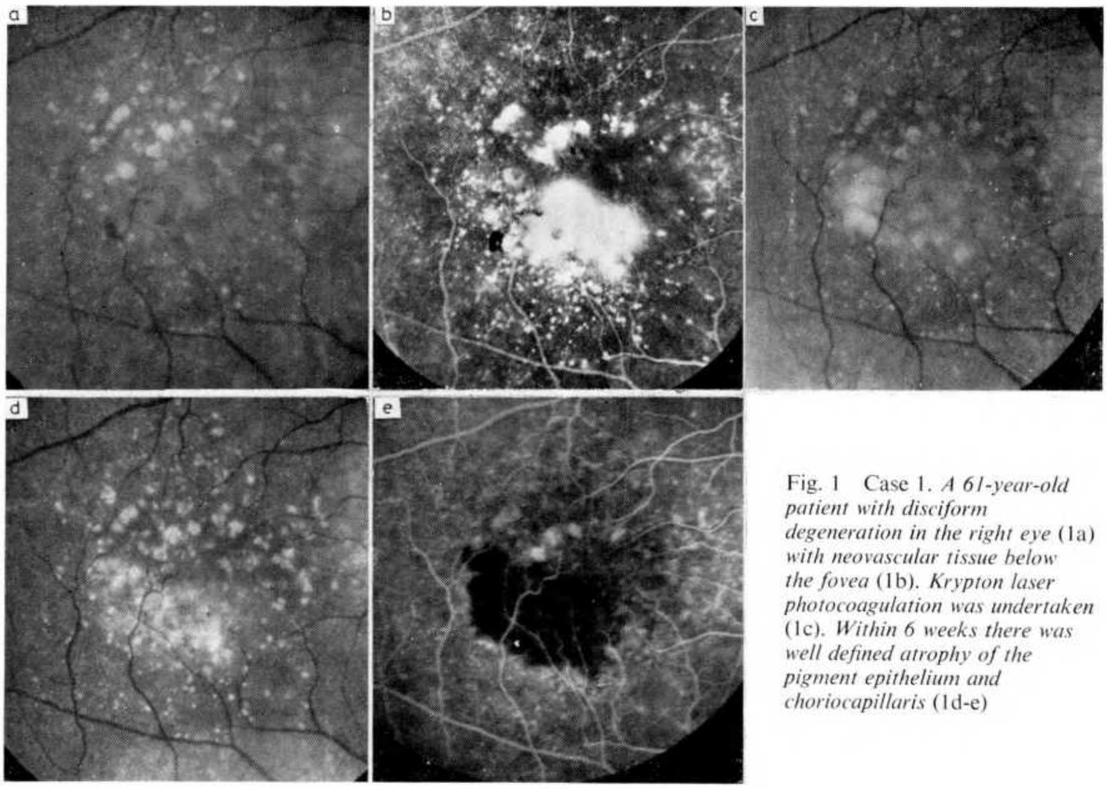

Fig. 1 Case 1. *A 61-year-old patient with disciform degeneration in the right eye* (1a) *with neovascular tissue below the fovea* (1b). *Krypton laser photocoagulation was undertaken* (1c). *Within 6 weeks there was well defined atrophy of the pigment epithelium and choriocapillaris* (1d-e)

was 0·2 to 0·5 second. Coagulation was contiguous over the whole lesion and for at least 100 μm beyond the limit of the neovascular tissue. One patient was treated twice (case 1) and the rest once. The progress of the lesion was reviewed at regular intervals by fluorescein angiography for at least 6 months after therapy.

Results

Of the 10 lesions treated, 7 became flat after photocoagulation and remained so for 6 months, 1 became flat but there was recurrent growth of new vessels 4 months after initial therapy (case 4), and in 2 there was recurrent growth of neovascular tissue immediately after photocoagulation (see Table 1). Of those patients successfully treated 6 retained or regained an acuity of 6/12 or better.

During therapy the photocoagulation lesions appeared to be confined to the deep retina and pigment epithelium however close to the fovea the lesions were placed (Figs. 1 and 2). Even some distance from the fovea the lesions appeared to affect less of the retinal thickness than occurs with argon, giving the impression of a lighter burn (Figs. 1 and 2). It was also possible to obtain coagulations beneath parafoveal blood vessels by directing the beam through the blood vessels without uptake of energy in the inner retina or alteration of vessel calibre.

During the postoperative period choroidal and pigment atrophy occurred early (Figs. 1 and 3); infarction of retina due to vascular occlusion and intraretinal fibrosis was not seen during the period of review. In all the postphotocoagulation angiograms the site of treatment appeared dark, however long after therapy the angiogram was undertaken. At no stage was there hyperfluorescence due to transmission defect, though the large choroidal blood vessels were sometimes outlined in the outer layers of the lesions (Fig. 3).

Discussion

The differences between the parafoveal lesions produced by argon (488 and 514·5 nm) and krypton (647 nm) wavelengths, which might have been predicted from theoretical data and from histological studies (Marshall and Bird, 1979), were evident clinically. It is the universal experience of

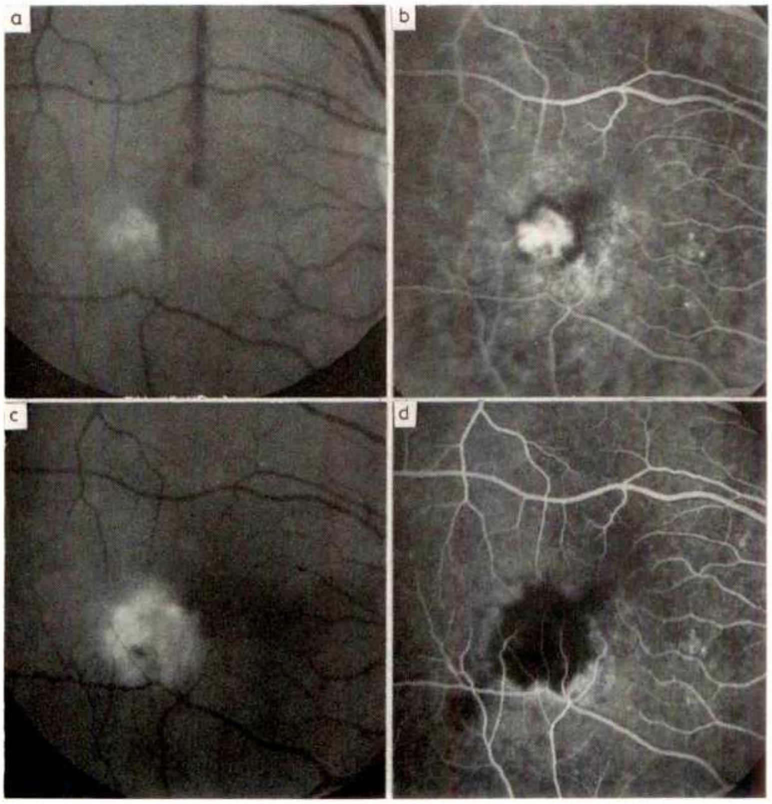

Fig. 2 Case 8. *A 76-year-old woman with a disciform lesion in the right eye* (2a) *with neovascular tissue below and temporal to the fovea* (2b). *Krypton laser photocoagulation was undertaken* (2c), *and within 4 weeks the neovascular tissue appeared to be obliterated* (2d)

therapists using argon laser energy that while approaching the fovea there is a sudden change in the morphology of the photocoagulation lesion. Away from the fovea the lesions are confined to the outer retina, but uptake by the inner retina near the fovea causes dense white swelling of the inner retina, obscuring the view of the subretinal structures. The fact that the inner retinal lesion is often larger than those at the retinal pigment epithelium, and that the site at which the change takes place is unpredictable, compounds the hazard of this phenomenon. By contrast, with krypton laser energy it is possible to approach the fovea slowly, expanding the lesion centrally in a controlled fashion, and the responses appear to be much more predictable. Thus the therapy itself was easier to deliver and control with the krypton than with the argon laser.

The manifest differences between the lesions produced by the 2 lasers as seen clinically are confirmed by histological studies (Marshall and Bird, 1979) and can be accounted for by the differential absorption of the 2 wavelengths by luteal pigment. On a theoretical basis it could be argued that krypton may have advantages over argon laser photocoagulation in the treatment of macular disciform lesions. If the failure of argon laser treatment of juxtafoveal lesions is due to inner retinal absorption of energy and consequent failure of energy delivery to subretinal structures, the longer wavelength of krypton would be a better therapeutic agent. Similarly, if destruction of parafoveolar receptors and bipolar cells which subserve foveolar function prejudices the visual outcome following argon laser photocoagulation, this problem would be obviated by using krypton. Furthermore, in some patients a poor visual outcome with the argon laser can be attributed to occlusion of macular venules and arterioles due to absorption of energy by the blood vessel. Such an accident would also be avoided with krypton. Finally in certain cases poor visual acuity following apparently successful treatment of a disciform lesion can be attributed to intraretinal fibrosis and gross distortion of the fovea. If this is due to inner retinal absorption of energy with or without vascular occlusion, a better postoperative visual acuity would be expected after krypton than after argon laser photocoagulation.

During the 6-month period after treatment the

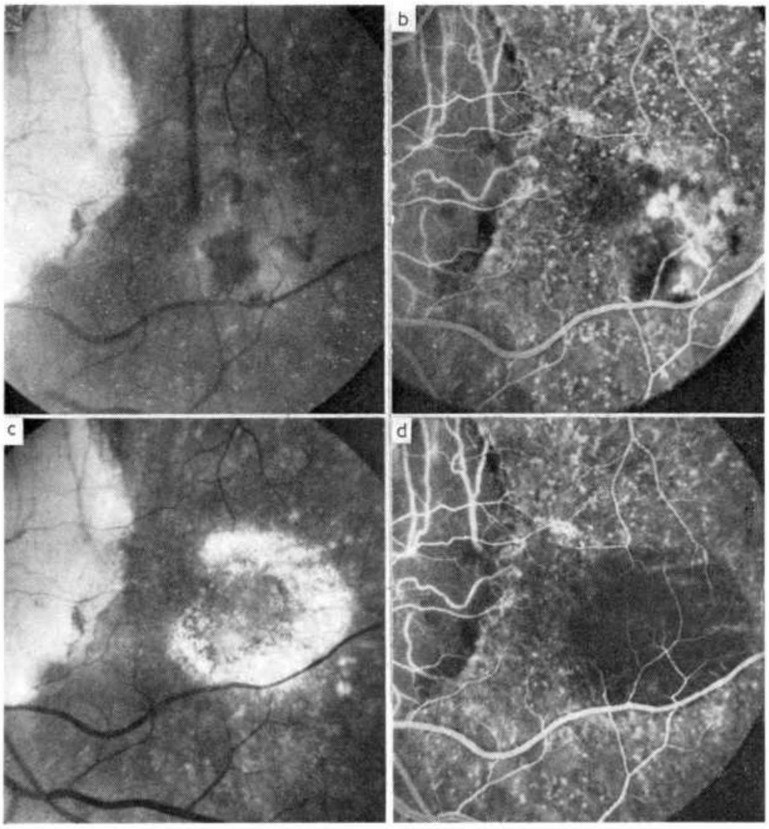

Fig. 3 Case 6. *A 71-year-old man, whose previous left eye disciform lesion had been successfully treated by argon laser photocoagulation 3 years before, had recurrence of the symptoms due to a new disciform lesion* (3*a*) *with neovascular tissue below and temporal to the fovea* (3b). *Six weeks later there was profound atrophy of the pigment epithelium and choriocapillaris* (3c, d)

lesions produced by the krypton laser differed from those following argon laser photocoagulation in some respects. The dark appearance during the first 2 weeks after therapy occurs with both lasers and can be ascribed to the masking effect of the swollen retinal pigment epithelium. The persistence of the darkness after this time, when the swelling had resolved, is likely to be due to confluent closure of the choriocapillaris. This impression is supported by the observation of well demarcated atrophy of the pigment epithelium within 6 weeks of photocoagulation and the observation of large choroidal vessels within the lesion during angiography. It is our impression that choroidal closure is more complete and seen more consistently after krypton than after argon laser photocoagulation. This impression is in accord with histopathological observations (Marshall and Bird, 1979). If as high a proportion as 85% of krypton energy passes into the choroid, this tissue may represent the site of maximum energy absorption. The effect of multifocal absorption by the choroidal melanosomes as opposed to the continuous absorption by the melanin in the apical portion of the retinal pigment epithelial cells was not apparent. The high energy density of absorption which might be expected by the choroidal melanosome would predictably give rise to haemorrhages due to blood vessel wall necrosis (Marshall and Bird, 1979), but this was not observed in these patients. However, the number of cases observed was small, and in a larger sample this complication might become apparent. Within the lesions observed the choroidal closure was complete, suggesting that the effect of the absorbed energy was similar to that which might be seen had the choroid been a continuous absorbing medium.

The clinical effect of the greater energy uptake in the choroid by krypton laser energy and more consistent choroidal vessel closure is difficult to predict. It could be argued that occlusion of choroidal blood vessels from which the abnormal neovascular tissue is derived may give rise to a greater cure rate, but may infarct pigment epithelium and receptors outside the irradiated area.

The success rate and visual outcome using krypton cannot be compared with that of argon with such a small sample. However, it is clear that disciform lesions can be treated successfully with the krypton laser with good visual results even if the neovascular tissue approaches close to the fovea. The relative merits of the 2 lasers as therapeutic agents can be assessed only by controlled clinical trial. If the trials which are under way at present show that there is any benefit derived by the treatment of disciform lesions by argon laser photocoagulation, a trial to compare the 2 modalities would be justified.

We express our gratitude to Lasertek for lending us their krypton laser which allowed us to undertake this study. I would also like to thank Miss J. Bramley for secretarial assistance and Mr K. Sehmi for photographic expertise.

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Argon laser photocoagulation in the treatment of central serous retinopathy

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SUMMARY In a prospective randomised trial of argon laser photocoagulation in the management of central serous retinopathy it was confirmed that this treatment hastens resolution of the serous detachment. No evidence was found to suggest that treatment influences the final visual outcome in eyes with initial visual acuity of 6/12 or better.

Although the pathogenesis, clinical features, and natural history of central serous retinopathy (CSR) have been more clearly defined in recent years, the indications for treatment are not precisely established. While many forms of therapy have been advocated, the benign nature of the condition and its tendency to recover spontaneously make their critical evaluation difficult. The predilection of CSR for young males, its tendency to persist for long periods, and the high recurrence rate make effective treatment desirable.

The ability to demonstrate the source of subretinal fluid in CSR by fluorescein fundus angiography (Maumenee, 1965; Gass, 1967), together with development of more sophisticated photocoagulation techniques (Wessing, 1971), suggested that an effective method of treatment might be available. Recent studies have shown that photocoagulation causes rapid resolution of the serous retinal detachment with symptomatic recovery (Spalter, 1968; Peabody *et al.*, 1968; Watzke *et al.*, 1974; Nanjiani, 1977).

On the basis of clinical impression it is acknowledged that photocoagulation can be justified if corrected visual acuity is worse than 6/12 (Hogan, 1974) or 0·8 (Wessing, 1974), if it is a second attack in the eye in question, and if there has been a permanent loss of acuity in the fellow eye from central serous retinopathy (Gass, 1974a). If the corrected visual acuity is good, some clinicians do not treat the condition (Hogan, 1974; Schoch, 1974; Klein *et al.*, 1974), while others recommend therapy if there are morphological changes in the detached retina, or if the symptoms interfere significantly with life (Wessing, 1974), though symptoms may persist after retinal reattachment and may never fully resolve (Gass, 1974b; Zweng, 1974).

In the common situation when these indications are absent it has been suggested that photocoagulation can be justified 2 or 3 months (Amalric, 1974; Gass, 1974a; Nanjiani, 1977) after the onset of symptoms. Such a recommendation can be sustained only if it is shown that the length of detachment determines the final visual outcome. To test this we undertook a prospective randomised trial of treatment with argon laser photocoagulation to discover how the natural history of CSR is modified by treatment and the effect of this on the visual outcome.

Definition. Central serous retinopathy was defined as a localised serous detachment of the retina occurring at the posterior pole in young people, for which no predisposing cause could be found. Serous retinal detachments associated with other identifiable lesions, such as tumours, inflammation, or congenital pits of the optic disc and generalised disease of the retinal pigment epithelium (RPE), were excluded, although multiple RPE defects were frequently present at the posterior pole in both eyes.

Patients and methods

Sixty-seven consecutive patients referred to the Retinal Diagnostic Department at Moorfields Hospital, City Road, London, with CSR were entered in the study having satisfied the following criteria: (1) corrected visual acuity 6/12 or better; (2) retina detached at macula; (3) RPE defects smaller than 1 disc diameter; (4) no symptomatic improvement since onset; (5) no subretinal exudates present; (6) no cystic retinal oedema present; (7) no associated ocular disease (e.g., drusen, congenital pit of the disc, generalised RPE dystrophy, etc.); (8) consent to participate in the study after explanation of aims and methods.

Patients were allocated to 4 groups, by drawing

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randomised cards from sealed envelopes, according to age (39 years or less; 40 years or more) and time of presentation (shorter or longer than 1 month after onset of symptoms). Half the eyes in each group were left untreated, and in the remainder treatment was carried out as soon as fluorescein angiograms were available. It was ruled that eyes in the untreated group in which corrected visual acuity fell to less than 6/12 during the study or which developed cystic retinal oedema or subretinal exudates should be treated and classified as failed conservative management.

The Coherent Radiation 800 argon laser was used for treatment after fluorescein angiographic labelling of the leaking site. Direct treatment to the leaking spot was carried out with burns of 50 to 200 μm in diameter, unless the leak was immediately subfoveal, when some 5–7 burns were applied within the lower margin of the serous retinal detachment (2 cases). Intensity and duration of the laser burns varied between 150 and 400 milliwatts and 20 and 200 milliseconds.

Patients were reviewed at approximately weekly intervals for 4 weeks and then at monthly intervals until symptoms improved, the retina flattened, and there was no identifiable leakage on fluorescein fundus angiography (FFA). Thereafter examinations were carried out at 3- and 6-monthly intervals.

Symptoms of central visual disturbance, in particular micropsia and metamorphopsia, were recorded at each visit, and the fundus was examined with the binocular indirect ophthalmoscope, slit lamp, and Hruby lens. Visual function was assessed by the best corrected Snellen visual acuity at each visit, while colour and fluorescein photography were undertaken in all cases at presentation and resolution and at other times when it was considered helpful. In 51 eyes the Farnsworth Munsell 100-hue test was carried out at each visit. Further investigations with the Amsler Chart, Nagel Anomaloscope, and electrodiagnostic studies were undertaken in some cases.

Of the 67 patients entered 4 had to be withdrawn, 3 because of failure to attend for follow-up examination and 1 who developed a disciform lesion. There were 53 males and 10 females, their ages ranging from 25 to 53 years with a mean of 40·1. The period of time between onset and presentation varied from 2 days to 35 weeks, with a mean of 5·6 weeks. Fifty-six of the patients were Caucasians, 9 were Asians and 2 Negroes.

Results

In all 67 eyes serous retinal detachment was associated with a demonstrable leak of fluorescein dye through the retinal pigment epithelium. In 35 patients (49%) transmission defects in the RPE were also found or there was a clear history of similar attacks previously in the same eye.

RECOVERY TIME

Complete recovery as shown by resolution of symptoms, reattachment of the retina, and absence of dye leakage on FFA, occurred at a mean time of 6·2 weeks from entry into the treated group and 16·0 weeks into the control group ($P<0·001$).

VISUAL ACUITIES

Snellen acuities were converted to a simple numerical scale from 1 (6/4) to 5 (6/12). The mean acuity on presentation was 4·1 for the control group and 3·9 for the treated group of patients and improved to 3·1 and 2·9 respectively at 6 months (Table 1). A significant difference between the visual acuities of the treated and untreated eyes occurred at 2 months after entry but at no other time. The mean visual acuity of the fellow eyes was 2·8 (Table 1, Fig. 1). Nine patients failed to achieve a final acuity of 6/6 or better. Six of these were in the control group and 3 were in the treated group; in all these cases the final acuity was 6/9. In no instance was it necessary to withdraw a patient from the trial because of a fall in visual acuity to less than 6/12.

HUE DISCRIMINATION

At entry the mean of the 100-hue scores in the control group was 212 and in the treated group 282, improving to 137 and 156 respectively at 6 months. No significant difference between the mean scores of the 2 groups was found at any stage (Table 1). The mean 100-hue score of the fellow eyes was 90.

Table 1 *Change in the mean visual acuities and Farnsworth Munsell 100-hue scores in the treated and control groups from the time of entry into the trial. Visual acuity; 1—6/4, 2—6/5, 3—6/6, 4—6/9, 5—6/12*

Interval after entry to trial	*Snellen acuity*			*F-M 100-hue*		
	Controls	*Treated*	*P*	*Controls*	*Treated*	*P*
On entry	4·1	3·9	0·245	212	282	0·117
2 weeks	4·1	3·9	0·206	189	243	0·200
4 weeks	4·0	3·6	0·106	159	149	0·819
2 months	3·7	3·1	0·003	178	149	0·533
3 months	3·5	3·1	0·089	160	101	0·145
6 months	3·1	2·9	0·211	137	156	0·718
>6 months	3·2	2·9	0·167	154	132	0·621
Fellow eyes		2·8			90	

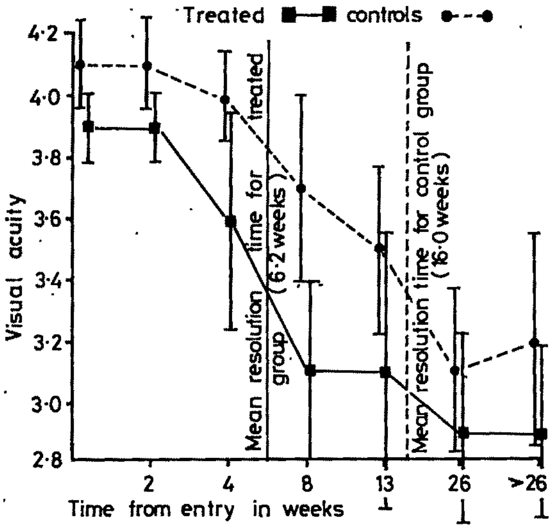

Fig. 1 *Visual acuity; 1—6/4, 2—6/5, 3—6/6, 4—6/9, 5—6/12. Graph showing the change in mean visual acuity of the treated and control groups from the time of entry into the trial*

INFLUENCE OF OTHER FACTORS

No significant difference was found between the visual acuities or 100-hue scores of the 2 groups when they were subdivided according to the patient's age, size of serous detachment, distance of fluorescein leak from fovea, or evidence of pre-existing RPE disease.

Discussion

In the 2 groups of patients studied the results of visual acuity testing with the Snellen chart closely paralleled the Farnsworth Munsell 100-hue scores, and there was a clearly demonstrable deficit in affected compared with fellow eyes. However, in an individual case it was often difficult to detect this with the Snellen chart, while the sensitivity and measurability of the 100-hue test demonstrated it easily. This difference between the 2 methods of assessing visual morbidity was particularly clearly seen when comparing the final visual acuities of the 2 groups with those of the fellow eyes, when no significant difference was found in the Snellen acuities, while there was a marked difference in the 100-hue scores. This observation correlates well with the experience of many patients who complain of mild symptoms long after clinical signs have resolved completely.

The severity of the visual deficit associated with CSR is due in part to hypermetropia and astigmatism and in part to receptor dysfunction induced by the serous retinal detachment. Although visual acuity can usually be improved with correcting lenses, correction of the refractive error is neither an easy nor a practicable treatment, because the refractive change is at best temporary and at worst fluctuating. Treatment aimed at achieving retinal reapposition, thus correcting both the refractive error and restoring normal receptor function, may therefore be justified.

It is accepted that photocoagulation is effective in causing retinal reapposition, and the results of this study confirm that resolution occurs more rapidly after photocoagulation than it does in the absence of treatment. However, there seems little evidence to suggest that speedy reattachment of the retina confers any long-term visual advantage to the patient, since there was no significant difference in the final visual acuity between the treated and the untreated groups. Moreover, in no patient in this series did the visual acuity deteriorate to less than 6/12, thus necessitating withdrawal from the trial. We therefore conclude that no patient lost vision because treatment was withheld, and persistence of serous retinal detachment did not lead to progressive receptor loss.

If our patients are representative of the disease as a whole, we are led to the conclusion that persistence of CSR does not lead to progressive deterioration of vision in those patients in whom the initial acuity is 6/12 or better. This may be explained if the degree of visual deficit is determined early in the disease or if the disease we have been studying is different from that in which serous detachment is accompanied by severe visual loss. The hypothesis that poor visual recovery in CSR is due to progressive receptor cell attrition related to prolonged detachment has never been proved, and other factors such as choroidal or retinal pigment epithelial disease may be responsible.

If laser photocoagulation carried no visual morbidity it could still be argued that treatment is justifiable in all cases, but, however small the risk, potential complications are implicit in this form of treatment. There is danger of photocoagulating the fovea or of coagulating a macular venule or arteriole, resulting in foveal ischaemia and intraretinal fibrosis (Gass, 1972).

Finally, some authors have claimed that photocoagulation may precipitate a disciform lesion, with the serious threat to central vision that such a lesion carries (François *et al.*, 1975; Schatz *et al.*, 1977). While in most patients treatment with the argon laser can be safely undertaken, there is a small proportion in whom the proximity of the leaking point to the fovea or to the major blood vessels makes this procedure hazardous, and indirect treatment may not be a practicable alternative to photocoagulation of the leaking site itself.

We conclude from our observations that, while laser photocoagulation is a safe and satisfactory method of treatment in those cases with distressing symptoms, there is no evidence that it influences the final visual outcome in patients whose vision is 6/12 or better and where there is no evidence of structural retinal damage. Treatment can be justified when the visual deficit affects the quality of life, particularly ability to work, but not on the basis of length of detachment alone. It should be possible to make a decision concerning treatment at the onset of the disease, as there is no evidence to suggest that the prognosis is influenced by the duration of serous detachment.

We are grateful to the consultant surgeons at Moorfields for allowing us to study their patients and to Professor A. C. Bird for his help and encouragement in the preparation of this paper. We thank Mr Hugh Donovan of the Computer Section, Institute of Ophthalmology, Judd Street, London WC1, for the statistical analysis of our findings, Mr T. Tarrant for preparing the figure, and Miss Christine Giffen and Miss Heather Lucas for drafting the manuscript.

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Association of juvenile disciform maculopathy with HLA B15

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SUMMARY Twenty patients with juvenile disciform maculopathy (JDM), which clinically cannot be differentiated from presumed ocular histoplasmosis, are presented. Histocompatibility antigen typing showed an increase in HLA B15, but this increase was not significant with respect to the *corrected* P-value. We are reporting our results in the hope of encouraging those who have cases of JDM in Europe to consider histocompatibility antigens and in particular HLA B15.

The HLA antigen distribution in 20 patients with juvenile disciform maculopathy (JDM) is presented and compared with the HLA typing of a very similar disease, namely, presumed ocular histoplasmosis. Juvenile disciform maculopathy is a clinical entity and patients with JDM show the following characteristics: haemorrhagic disciform detachment of the macular or perimacular region; small well-defined choroidal or pigment epithelial lesions of the posterior pole or at the papillary margin; no involvement of the anterior segment; clear vitreous; prevalence mainly in the age group of 20 to 40 years; negative histoplasmin skin test.

The disease has many names—for example, haemorrhagic exudative retinitis (Hausschild, 1974), ocular histoplasmosis syndrome (Braunstein *et al.*, 1974), multifocal choroiditis (presumed histoplasmosis) (Notting *et al.*, 1975), focal haemorrhagic choroiditis (Schildberg and Wessing, 1975), juvenile haemorrhagic maculopathy (Oosterhuis *et al.*, 1976), and juvenile haemorrhagic macular degeneration or 'histoplasmosis-like choroiditis' (de Laey, 1978).

In effect all these are cases of JDM and cannot be differentiated from presumed ocular histoplasmosis on the clinical picture alone. Since *Histoplasma capsulatum* is rarely seen in Europe (Ellis and Schlaegel, 1973), and since patients with JDM have negative histoplasma skin tests, the relationship with histoplasma must be questioned.

Materials and methods

On the basis of the characteristics listed above 20 patients with JDM were selected, all being confirmed by fluorescein angiography. The patients were otherwise healthy, young (average age 35, range 14 to 42 years), and had been observed for an average of 3·9 years (range 0·25 to 8 years). From each of the 20 patients 20 ml of freshly drawn blood was heparinised (2 drops of Thromboliquine) and sent within hours to the HLA typing laboratory of the Department of Immunohaematology at Leiden University.

HLA typing was performed according to the National Institutes of Health lymphocyte microcytotoxicty technique (Ray *et al.*, 1976) with a set of 120 typing sera. A group of 4000 healthy Dutch blood donors served as a control population for the HLA A and B specificities. Out of this group 1824 were also typed for HLA C locus groups Cw1 to 5.

Results

Among the 20 cases of JDM 29 HLA A, B, and C locus specificities could be defined (Table 1). An increase in HLA B15 was observed in 8 patients (40%) as compared to 15·7% in the control group. These patients, 3 males and 5 females, with an average age of 35 years (range 15 to 42 years) were observed for an average duration of 3·2 years (range 0·25 to 5 years). All patients had reached the inactive scar stage with the exception of 1 male, who after 3 months' observation still showed an active subretinal neovascularisation. The increase in HLA B15 when compared with the control population gave $\chi^2=7\cdot76$, $P=0\cdot00534$, $RR=3\cdot6$, and corrected $P=0\cdot14$ (Woolf, 1955; Edwards, 1974). The uncorrected P value is just significant, whereas the corrected P value is not.

In presumed ocular histoplasmosis the frequency of the HLA B7 antigen was shown to be statistically

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Table 1 *HLA antigen distribution in patients with juvenile disciform maculopathy and in controls*

	Patients n = *20*		*Controls* n = *4000*	
	Number	*Per cent*	*Number*	*Per cent*
HLA A1	5	25	1254	31·3
A2	11	55	2141	53·5
A3	8	40	1222	30·5
A9	3	15	806	20·2
A10	2	10	275	6·9
A11	0	0	409	10·2
A28	1	5	375	9·4
Aw19	4	20	811	20·2
B5	5	25	410	10·2
B7	7	35	1175	29·4
B8	4	20	932	23·3
B12	3	15	1014	25·3
B13	0	0	196	4·9
B14	0	0	143	3·6
B15	8	40	627	15·7*
Bw16	1	5	256	6·4
B17	1	5	323	8·1
B18	2	10	258	6·4
Bw21	0	0	102	2·6
Bw22	0	0	210	5·3
B27	1	5	312	7·8
Bw35	5	25	698	17·4
B37	0	0	151	3·8
B40	1	5	705	17·6
			n = 1824	
Cw1	0	0	131	7·2
Cw2	1	5	318	17·5
Cw3	9	45	680	37·3
Cw4	6	30	501	27·3
Cw5	1	5	135	7·4

*χ^2 = 7·76 (Woolf, 1955)

significant (Godfrey *et al.*, 1978; Braley *et al.*, 1978). In our cases the HLA B7 antigen occurred in 7 cases, 3 males, and 4 females, average age 37 years (range 24 to 46 years) and were observed during 4·6 years (range 3 to 7 years). All 7 cases have arrived in the inactive scar stage and have shown no activity during the last year.

The frequency of HLA B7 in JDM was 35% as compared to 29·4% in the control group and falls within normal limits.

Discussion

The clinical features of JDM have been recognised in Europe for at least 10 years. Even in the USA 11% of the patients with presumed ocular histoplasmosis have negative skin tests (Ellis and Schlaegel, 1973). These may be cases of JDM.

Recent publications have shown a statistically significant increase in the frequency of HLA B7 antigen in cases with the presumed ocular histoplasmos syndrome (Godfrey *et al.*, 1978; Braley *et al.*, 1978). The HLA B7 frequency was not significantly increased in our cases of JDM.

Flaage *et al.* (1977) found no specific HLA antigen frequencies in their 9 cases of juvenile haemorrhagic maculopathy. In our 20 cases of JDM an increase in HLA B15 is not significant with respect to the corrected P value, but it is certainly worthwhile continuing to determine the histocompatibility antigens in cases of JDM.

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The inferior oblique as muscle of choice for biopsies of extraocular muscles

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SUMMARY Suitable biopsies can easily be taken from the inferior oblique muscle without unwanted side effects from the belly of this muscle, allowing complete examination by light and electron microscopy. The inferior oblique is the muscle of choice for biopsy studies of extraocular muscle.

Investigations performed on biopsy material from limb muscles have contributed greatly to knowledge of neuromuscular diseases. Extraocular muscles (EOM) are distinct from other skeletal muscles in physiological, morphological, and histochemical respects (Hess and Pilar, 1960; Harker, 1972; Peachy *et al.*, 1974; Durston, 1974; Ringel *et al.*, 1978). Biopsies from EOM in ophthalmoplegia have been investigated only occasionally, however.

There are at least three reasons for this reserved attitude. Firstly, it is imperative to exercise caution in performing eye muscle biopsy so that ocular motility is not impaired (Ringel *et al.*, 1978). The physician in charge is often not familiar with eye muscle surgery and may be anxious about ocular motility. Secondly, whereas the muscle belly is the most suitable part in the muscle for biopsy purposes (Dubowitz and Brooke, 1973), most EOM bellies lie deep in the orbit and are not easily accessible. Thirdly, pathological changes in EOM differ in many respects from those in limb muscles, and their evaluation is difficult because many criteria applicable to limb muscles cannot be used (Drachman *et al.*, 1969; Goebel *et al.*, 1974; Harriman, 1975).

The aim of the present paper is to demonstrate that the inferior oblique is the muscle of choice for EOM biopsies. Sufficient material for adequate morphological and histochemical investigations can be taken from this muscle without unwanted side effects.

Table 1 *Clinical details of patients*

Patient	*Sex*	*Side*	*Age (yr)*	*Light microscopy*	*Electron microscopy*	*Clinical diagnosis*
1	M	R	6	+		Congenital oculomotor weakness
2	M	L	21	+	+	Mitochondrial myopathy
3	M	L	25	+	+	Exophthalmus
4	M	L	30	+		Dystrophia myotonica
5	M	R	48	+		Hereditary ataxia
6	M	R	48	+	+	Ocular myasthenia
7	M	R	51	+		Ocular myopathy
8	M	L	52	+	+	Ocular myasthenia
9	M	L	61	+	+	Ocular myasthenia
10	M	L	72	+		Ocular myasthenia
11	F	R	54	+	+	Atrophia faciei
12	M	R	31	+	+	Ocular myopathy
13	M	L	55	+	+	Ocular myasthenia
14	M	R	47	+	+	Ocular myasthenia
15	M	R	50	+	+	Oculomotor paralysis
16	M	R	35	+	+	Ophthalmoplegia plus

Material and methods

Biopsies from inferior oblique muscle were taken in 16 patients. All these patients had complaints of ptosis or diplopia (Table 1), and all had been examined ophthalmologically and neurologically. Biopsy was recommended when it was considered likely that the examination might yield information to aid diagnosis and treatment. Every patient was given an outline of the procedure in advance. The biopsy was preferably taken under local anaesthesia, but in 5 cases it was performed during a surgical

Address for reprints: Dr T. U. Hoogenraad operation for ptosis or strabismus done under general anaesthesia.

SURGICAL TECHNIQUE

Good accessibility of the distal half of the inferior oblique muscle is obtained by rotating the eyeball inwards and upwards. The muscle is approached by a horizontal incision in the inferior temporal quadrant of the conjunctiva and Tenon's capsule, just above the upper margin of the muscle. The muscle fascia is dissected bluntly. The muscle is engaged under direct vision with the help of 2 muscle hooks, and 10 to 15 mm of the inferior oblique is exposed in this way. A double-ended clamp is placed on the upper part of the muscle. The distance between the 2 ends of the clamp is 4 mm. A second and smaller clamp (distance between the clamp ends 2 mm) is placed next to the first one. The muscle is cut on both outer sides of the clamps, and the segments, still held in the clamps, are excised. The muscle is now allowed to retract and the conjunctival incision is closed by suture.

LABORATORY TECHNIQUE

The specimen held in the larger clamp is frozen in isopentane, cooled in liquid nitrogen and is transferred to a cryostat. The frozen specimen is freed from the clamp with a goldsmith's fretsaw (Miller, 1967). The specimen is mounted on a small piece of cork and orientated as an upright cylinder. Transverse sections may now be cut and stained by routine histological and histochemical methods. The specimen held in the small clamp is placed immediately in an ice-cold cacodylate-buffered 2% glutaraldehyde solution.

After 10 minutes the clamp is opened and the specimen is divided into smaller pieces. It is prepared for electron microscopy according to standard methods.

Results

After biopsy all patients were examined regularly for 14 days. No unwanted side effects were observed. Patients operated on only for biopsy found the procedure to be not very painful. Minor discomfort was reported during the first days after operation. None complained of increase of diplopia. Examination showed no increase of weakness of the inferior oblique muscle.

The cryostat sections were approximately 2×2 mm. They confirmed that the biopsy had been taken from the fleshy part of the muscle. The sections contained tissue from both peripheral and central parts of the muscle (Figs. 1 and 2). Sufficient material for 2 histological stainings and 5 to 10 histochemical techniques was available, and in all cases the stainings could be repeated once or several times in fresh sections when this was needed.

The size of the cryostat sections from Case 2 was insufficient for adequate histological and histochemical investigations. Sections from this material contained approximately 100 fibres. Tissue from 11 patients were fixed and embedded for electron microscopy. Some artefactual damage of the specimen was present, but adequate examination was possible in all cases (Figs. 3 and 4).

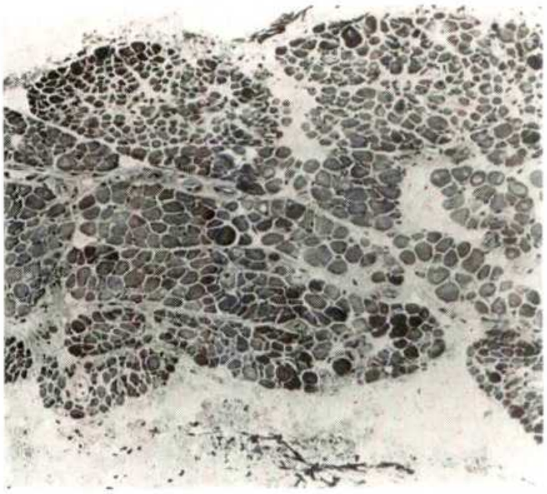

Fig. 1 *Case 15. Clinical diagnosis: oculomotor paralysis. Inferior oblique muscle. Peripheral and central areas in cross-section. Frozen section. Haematoxylin and eosin (×80)*

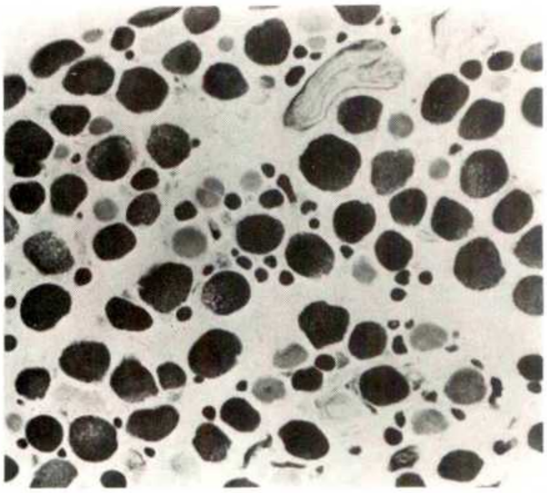

Fig. 2 *Case 1. Clinical diagnosis: congenital oculomotor weakness. Inferior oblique muscle. Central area. Frozen section. Myosin—ATPase, pH 9·4 (×240)*

Discussion

An account of the first biopsy study of extraocular muscles was published more than three decades ago by Sandifer (1946). He used material from the external rectus muscle, and his example was followed by most other authors. Only a few studies on the inferior oblique muscle have been reported (Schlote and Körner, 1975; Mukuno *et al.*, 1976; Hoogenraad *et al.*, 1977). Initially we also used the external rectus for biopsy.

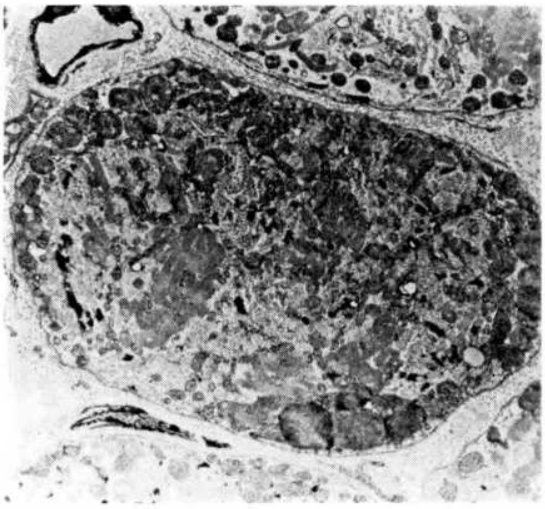

Fig. 3 *Case 2. Clinical diagnosis: mitochondrial myopathy. Inferior oblique muscle. Electron microscopy (× 3200)*

The results were usually disappointing, as the biopsies often contained predominantly fibrous and tendinous tissue and relatively few muscle fibres. We suggest that for at least three reasons the inferior oblique muscle is to be preferred for biopsy studies of EOM. Firstly, it has been shown that the inferior oblique is highly resistant to weakening by myectomy. Helveston (1973) reports that in stabismus surgery large muscle resections may be done and even subtotal myectomies without crippling the muscle. Secondly, the tendinous part of a muscle is not suitable for biopsy examination. The inferior oblique is unique in having an extremely short tendinous ending, so being fleshy throughout nearly all its length. According to Crone (1973) the length of the tendon is less than 1 mm in the inferior oblique but varies between 3·7 and 30 mm in other EOM. Thirdly, the belly of the inferior oblique, in contrast to that of other EOM, is easily accessible, as it lies in the anterior part of the orbit.

The results presented in this paper and case studies reported elsewhere (Hoogenraad *et al.*, 1977; Hoogenraad *et al.*, 1978) show that investigations of large numbers of fibres are readily undertaken

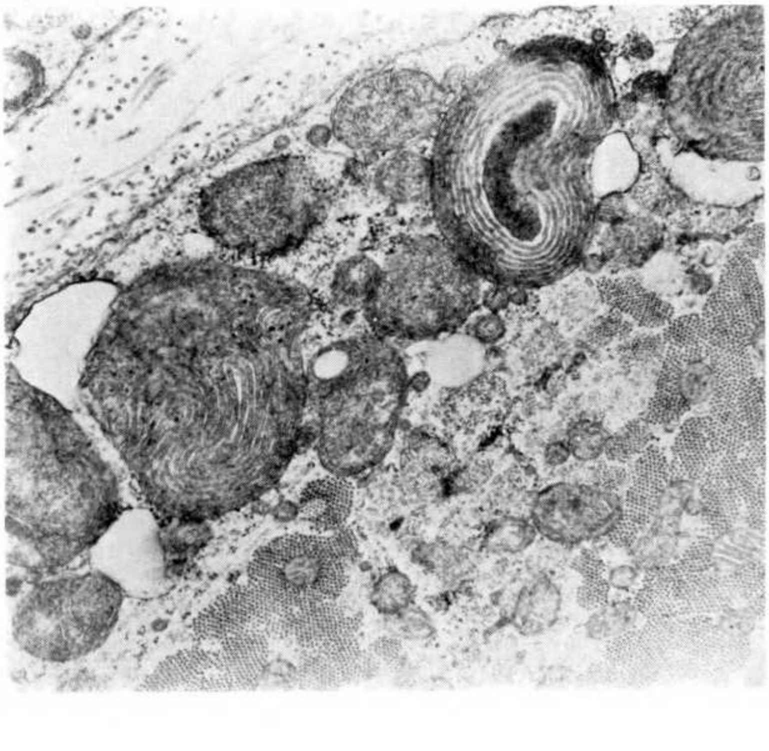

Fig. 4 *Case 2. Clinical diagnosis: mitochondrial myopathy. Inferior oblique muscle. Electron microscopy (× 8500)*

with all currently used morphological and histochemical techniques in the peripheral and central zones of inferior oblique biopsies. Data on the histology and the histochemical fibre types in this muscle are available (Hoogenraad *et al.*, 1979).

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Tissue response to the Fadenoperation

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SUMMARY The Fadenoperation was performed on 24 rabbit eyes. In 8 eyes the globe and muscle were removed intact and in 16 eyes the muscle was dissected from the sclera to determine the site and degree of attachment. The greatest degree of adherence was found between the muscle and the sclera at the site of the suture, less attachment at the lateral and medial border of the muscle, less in the central area close to the suture site, and least in the central anterior area. The Fadenoperation creates adherence of the muscle to the sclera. Its clinical usefulness will, however, depend on clinical evaluation.

The Fadenoperation is a procedure designed to change the anatomical and thereby the functional arc of contact of a muscle by suturing the muscle to the sclera 12 to 18 mm posterior to its insertion (de Decker and Conrad, 1975; Muhlendyck and Linnen, 1975; Muhlendyck, 1976). It is suggested that this procedure will alter the deviation in the field of maximum deviation with no effect in the primary position, that is, the dynamic angle as differentiated from the static angle of strabismus. Neither the clinical effectiveness nor the nature of the tissue changes have been conclusively established. It is the purpose of this study to determine the tissue changes produced by this procedure.

Material and methods

A total of 24 eyes were investigated in 13 New Zealand white rabbits with an average age of 18 months and an average weight of 4·4 kg. Topical tetracaine and 20 mg/kg of sodium pentobarbital was used for anaesthesia. A traction suture was placed at the inferior limbus, a fornix-based conjunctival flap was raised, and the inferior rectus muscle isolated. The inferior rectus was chosen since it is thicker than the horizontal rectus muscles, so that subsequent evaluation is easier. The inferior oblique was isolated and dissected free of the inferior rectus. Two 5–0 Merseline sutures were used to secure the muscle to the sclera about 8 mm posterior to the insertion. The suture was passed through the sclera and then through the muscle 2 mm from the border and tied. Indian ink was used to mark the sclera anterior to the muscle. This technique proved useful in identifying the site of muscle insertion and for the technician in preparing the sections. The conjunctiva was reattached at the limbus.

The eyes were re-examined an average of 81 days after surgery. Twenty-four muscles in 13 rabbits were reviewed. In 8 eyes the globe and the muscle were removed intact, sectioned, and stained with trichrome. In 16 eyes the muscle was redissected to determine the nature, site, and strength of scleral attachment. In several dissected eyes the eyes were sectioned and stained with trichrome subsequent to the dissection.

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Results

On exposing the inferior rectus the first observation was that it was not possible to pass a strabismus hook under the margins of the muscle anterior to the suture, even if a sharp-tipped strabismus hook was used. On a 1- to 4-scale the adherence was graded 4+ at the suture site and 3+ along the margins of the muscle. This pattern of adherence was evident in all the muscles dissected (Fig. 1).

Of those eyes that were dissected 6 were dissected from the suture toward the limbus. The adherence was graded as 1+ anteriorly in the centre and 2+ posteriorly in the centre (where a strabismus hook could be passed from behind forwards between the sutures with only slight effort). In 1 eye the anterior centre was probably free of the tenuous anterior centre adhesion. In 10 eyes the muscle was dissected from the insertion toward the site of the suture. In 7 eyes the same distribution of adherence was noted.

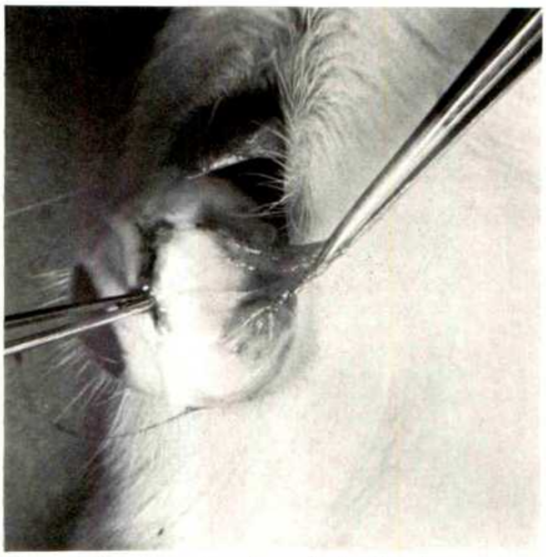

Fig. 1 *Blunt dissection of muscle showing the greatest adherence of the muscle to the sclera at the suture site and less adherent along the side of the muscle*

In 3 eyes the central anterior area of the muscle was apparently not adherent. Two of these eyes, however, were the first to be redissected, and it is possible that we failed to observe the adhesion, which was very tenuous. The third eye was dissected only 10 days after the original surgery. The dissected eyes were sectioned and stained with trichrome and showed muscle fibres adherent to the sclera after blunt dissection (Fig. 2).

In those eyes removed with the muscle attached without dissection and examined histologically the muscle was found to be adherent to the sclera (Fig. 3). The area around the suture showed a foreign body reaction with the most intense fibrous connective tissue adherence to the sclera. In general this method of examination yields little indication of the degree of adherence.

Discussion

The clinical effectiveness of the Fadenoperation has yet to be determined. It has been recommended in cases with a variable angle of strabismus, nystagmus,

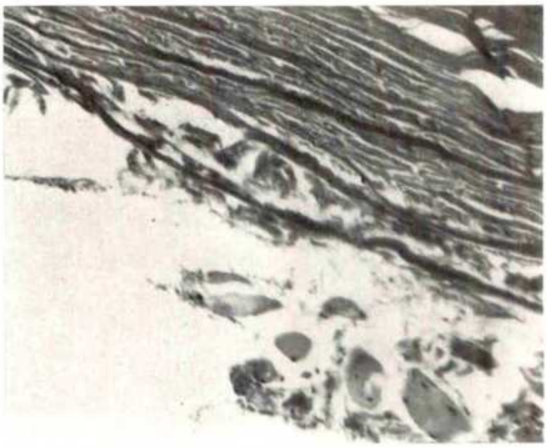

Fig. 2 *Muscle fibres remaining adherent to the sclera after bluntly dissecting the muscle anterior to the suture*

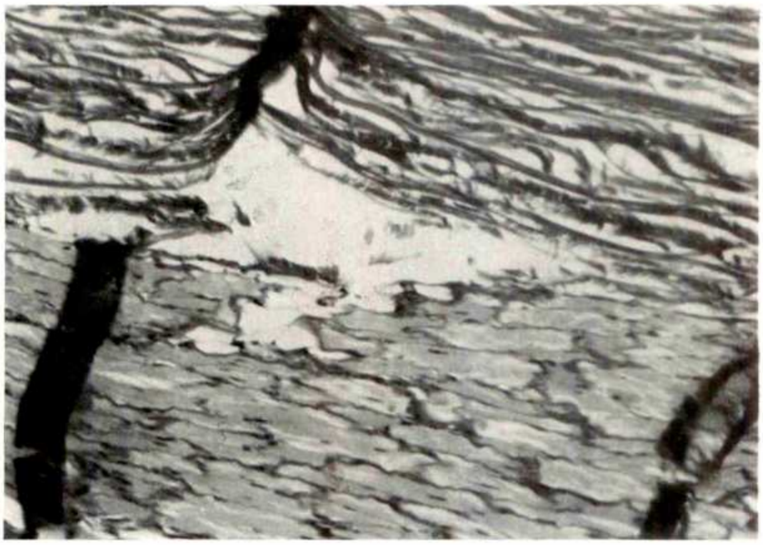

Fig. 3 *Undissected globe showing adherence of muscle to sclera anterior to the suture site*

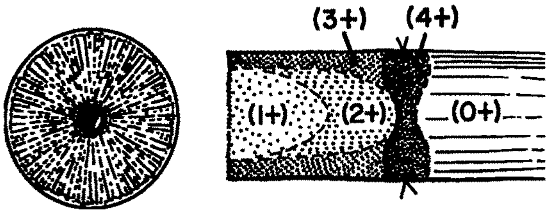

Fig. 4 *Diagrammatic representation of the distribution and strength of adherence—4+ represents the greatest adherence and 1+ the least adherence*

and in dissociated vertical deviations. Most of the cases reported by Muhlendyck and Linnen (1975) had standard horizontal muscle surgery as well as the Fadenoperation, which makes the results difficult to evaluate.

The procedure does indeed create an adherence between the muscle and the sclera. The greatest adherence is at the site of the suture, somewhat less at the lateral borders of the muscle and least in the anterior central portion (Fig. 4). The procedure does produce the intended anatomical changes, but its usefulness will depend on further clinical evaluation.

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The intraocular penetration of cefuroxime after parenteral administration

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SUMMARY Cefuroxime (Zinacef) is a new second generation cephalosporin which is resistant to β-lactamases produced by both Gram-negative and Gram-positive organisms, with an antibacterial spectrum that includes practically all likely ocular pathogens except pseudomonas. It is shown to penetrate into the eye after intravenous (1·5 g) or intramuscular (1 g) injection and achieve therapeutic concentrations, with absence of side effects. Cefuroxime is therefore a useful antibiotic for ophthalmic infections and should have a role in combination with gentamicin in intraocular infections, particularly those of unknown aetiology.

The devastating effect of severe bacterial infections of the eye and the development of resistant organisms to the antibiotics used demand that a constant appraisal be made of the ocular pharmacodynamics and pharmacokinetics of new antibacterial agents. There is often difficulty in isolating causative organisms in ophthalmology, and thus the search continues for broader spectrum and safer antibiotics.

Cephaloridine and cephalothin are effective broad spectrum injectable antibiotics. The penetration of cephaloridine (Riley *et al.*, 1968; Records, 1968, 1969a, 1969b; Richards *et al.*, 1972) and of cephalothin (Mizukawa *et al.*, 1965; Hatano *et al.*, 1966) into human aqueous has been studied after parenteral administration. It has been shown that adequate therapeutic levels of both these cephalosporins are achieved in the primary aqueous after injection, but cephaloridine shows superior ocular penetration and in addition gives less pain at the site of intramuscular injection.

The major defect of these first-generation cephalosporins is that they are hydrolysed by the β-lactamases of many Gram-negative bacteria. However, the newer cephalosporins such as cefamandole, cefoxitin, and cefuroxime (O'Callaghan, 1975) have a much broader spectrum of activity (Table 1), the 2 latter mainly because of a substantially increased resistance to many bacterial β-lactamases produced by a number of Gram-negative organisms.

Table 1 In-vitro *activity of cefuroxime*

Organism	*Sensitivity*
Gram-positive	
Staphylococcus aureus	+ + +
Streptococcus pneumoniae	+ + +
Streptococcus pyogenes	+ + +
Gram-negative	
Haemophilus influenzae	+ + +
Escherichia coli	+ +
Klebsiella pneumoniae	+ +
Proteus mirabilis	+ +
Pseudomonas aeruginosa	R

+ + + indicates MIC < 1 μg/ml.
+ + indicates MIC 1–8 μg/ml.
R indicates MIC > 125 μg/ml.

Axelrod and Kochman (1976) have studied the intraocular penetration of cefamandole in 7 patients who were undergoing elective cataract extraction. They showed that after an intravenous or intramuscular injection of 1 g, aqueous levels of up to 1·1 μg/ml were seen between 1·1 and 2·5 hours after injection, though in 2 of the patients no cefamandole was detected in the aqueous 4 hours after parenteral administration.

The purpose of this study was to determine the aqueous levels of cefuroxime after an intramuscular or intravenous dose in patients undergoing routine cataract extraction.

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Patients and methods

Sixty patients (27 male, 33 female; age range, 36 to 93 years) who were about to undergo cataract extraction were selected for study. After being informed of the nature of the study patients gave their informed consent to an additional procedure being carried out. Half the patients had their operation at the Oxford Eye Hospital and the others at the Royal Berkshire Hospital. A similar protocol was followed in each centre, the only difference being that in Oxford patients received cefuroxime (1 or 1·5 g) intravenously, whereas in Reading cefuroxime (1 g) was given intramuscularly.

All patients with a history of allergy were excluded from the study, and no patient received topical prophylactic antibiotics. Cefuroxime was administered between 0·5 and 6 hours before the time of aqueous tap.

After the patient had been anaesthetised and the eye prepared, before the opening of the anterior chamber, the globe was grasped over the medial rectus and the chamber entered with a fine aspiration needle (No. 27) on a Mantoux syringe through the presection groove. With the bevel down a sample of aqueous was removed (100 to 200 μl). The chamber was reformed with Ringer's saline, though the paracentesis wound and cataract surgery proceeded in routine fashion.

The aqueous sample was placed in a microcentrifuge tube, capped and labelled with a study number, and stored at –40°C. A simultaneous venous blood sample was taken, the plasma being removed for storage at –40°C until analysis.

Cefuroxime was assayed in the plasma and aqueous by the agar diffusion method using *Bacillus subtilis* 1904E as the assay organism.

Results

The details of the patients studied and plasma and aqueous levels of cefuroxime obtained are given in Table 2. Thirty patients received 1 g of cefuroxime by intramuscular injection, and the resulting aqueous levels measured between 0·5 and 6 hours after injection ranged from <0·3 to 2·2 μg/ml (Fig. 1), with a median value of 0·9 μg/ml. Eleven patients received 1 g of cefuroxime and 19 patients 1·5 g of cefuroxime intravenously. The median aqueous level measured between 25 minutes and 5 hours after administration by this route was 1·6 μg/ml (range, 0·5 to 3·1 μg/ml) for the 1·5 g dose and 1·7 μg/ml (range, <0·3 to 5·7 μg/ml) for the 1 g dose (Fig. 1). Thus, the cefuroxime levels in the aqueous humour were higher after intravenous than after intramuscular administration (Figs. 1 and 2), with the levels

Table 2 *Aqueous humour levels of cefuroxime after parenteral administration*

Patient	*Age (yr)*	*Sex*	*Time (h)*	*(min)*	*Plasma level (μg/ml)*	*Aqueous level (μg/ml)*
1 g IM						
1	65	F	—	30	17·8	—
2	77	F	—	45	35·3	—
3	65	F	1	—	27·0	0·8
4	78	F	1	—	5·8	0·5
5	72	F	1	—	25·6	0·5
6	68	F	1	30	29·7	<0·3
7	43	M	1	30	14·1	<0·3
8	65	F	1	45	43·1	0·9
9	72	M	2	—	12·3	<0·3
10	86	M	2	—	27·1	1·3
11	73	M	2	—	15·9	1·0
12	76	F	2	25	—	0·8
			2	30	36·7	—
13	78	M	2	30	15·2	0·8
14	—	F	2	35	32·3	0·9
15	73	M	2	40	24·6	1·0
16	86	F	2	45	—	1·8
17	77	M	3	—	21·1	—
18	64	F	3	—	12·6	0·7
19	73	M	3	15	7·8	1·1
20	73	M	3	15	<0·1	<0·3
21	75	M	3	15	25·3	1·7
22	69	F	4	—	12·7	<0·3
23	80	M	4	—	17·9	1·1
24	70	F	4	05	23·0	1·9
25	82	M	4	07	—	2·2
			4	17	30·9	—
26	74	F	4	30	19·8	1·4
27	73	F	4	30	12·0	1·8
28	77	F	5	—	7·9	—
29	64	—	5	30	8·9	1·1
30	78	M	6	—	8·5	0·9
1 g IV						
31	78	M	—	25	—	<0·3
32	85	F	1	10	39·1	1·3
33	88	M	1	25	66·5	5·7
34	79	M	1	25	49·5	1·1
35	80	F	1	25	33·1	—
36	83	M	1	40	50·7	2·1
37	93	F	1	55	57·0	0·7
38	87	F	3	05	19·1	1·8
39	90	M	3	10	23·3	—
40	36	M	4	—	—	<0·3
			4	45	4·7	—
41	68	F	5	—	11·9	1·7
1·5 g IV						
42	58	M	—	40	183·2	2·0
43	73	M	—	45	—	1·3
			—	50	127·4	—
44	83	F	—	48	36·2	—
			1	28	—	2·9
45	72	F	—	55	50·8	1·4
46	86	M	1	—	181·8	1·6
47	79	M	1	08	47·4	2·2
48	86	M	1	09	32·2	—
49	76	F	1	10	60·6	2·4
50	64	M	1	15	53·7	1·5
51	83	F	1	15	17·9	—
52	77	F	1	15	116·0	3·1
53	73	F	2	—	56·8	1·2
54	76	F	2	08	31·2	2·2
55	84	F	2	15	78·7	2·5
56	66	F	2	45	78·0	2·3
57	62	F	3	—	9·7	1·0
58	83	F	3	05	18·2	1·6
59	61	F	4	53	2·7	0·5
60	66	M	—	—	23·3	0·7

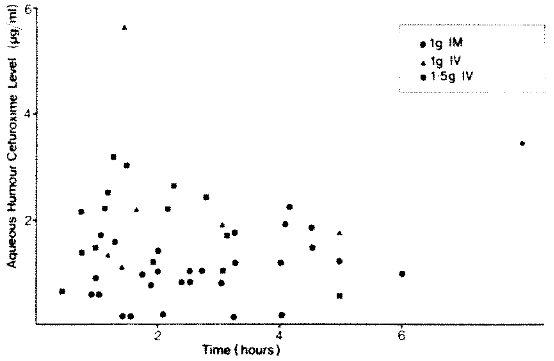

Fig. 1 *Aqueous humour levels of cefuroxime after parenteral administration*

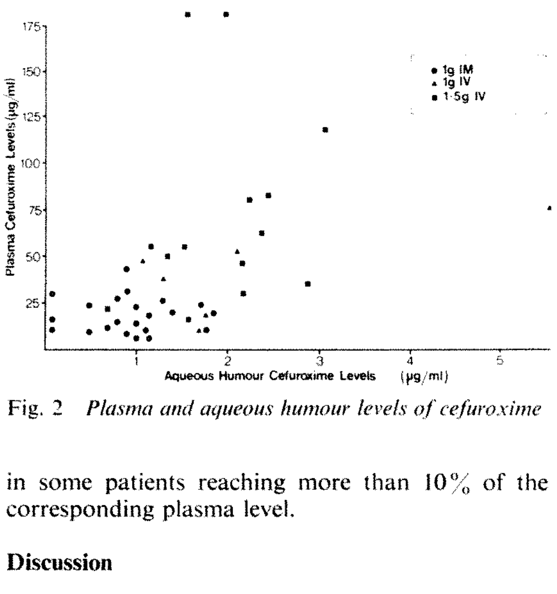

Fig. 2 *Plasma and aqueous humour levels of cefuroxime*

in some patients reaching more than 10% of the corresponding plasma level.

Discussion

This study shows that significant levels of cefuroxime are achieved in the primary aqueous after parenteral administration. The levels obtained are very much greater than the minimum inhibitory concentrations (MICs) of those organisms (O'Callaghan *et al.*, 1976) causing the majority of bacterial infections of the eye. In addition, this study was carried out in uninflamed eyes, and penetration will probably be higher under inflamed conditions (Richards *et al.*, 1972).

However, although cefuroxime should be of value in ophthalmology, its poor antibacterial activity against pseudomonas means that for severe corneal and intraocular infections when no causative organisms can be detected combination treatment with an aminoglycoside would be logical.

We have shown that higher aqueous levels of cefuroxime were achieved 2 or more hours after the intramuscular administration of 1 g compared with the first 2-hour period. Moreover, even higher levels were obtained when this dose or the 1·5 g dose were given intravenously. The conclusion can be drawn that to provide adequate antibacterial cover during ocular surgery an intravenous dose of 1·5 g cefuroxime should be given 1 to 2 hours before the operation begins.

A previous report of the intraocular penetration of cephaloridine commented on the usefulness of this cephalosporin in treating syphilitic patients (minimum immobilisation concentration against *Treponema pallidum* is 0·055 µg/ml). There are reports that after treatment with penicillin the survival of *Treponema pallidum* is favoured in the eye because of the poor penetration of penicillin into this site (Sparling, 1971). Cefuroxime, with its good intraocular penetration and high activity against this spirochaete (minimum immobilisation concentration of 0·0125 µg/ml), might therefore have an important role in the treatment of tertiary syphilis.

The authors thank Miss Susan Bristow for typing this paper.

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Systemic absorption of topically applied chloramphenicol eyedrops

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SUMMARY Five children under the age of 9 years had topical chloramphenicol drops administered 2-hourly to each eye for 5 to 7 days. Systemic absorption was not detected by 2 sensitive assays for the drug. The hazards of topical chloramphenicol and reports in the current literature are discussed.

Two cases of suspected bone marrow depression due to topical application of chloramphenicol eyedrops have been reported (Rosenthal and Blackman, 1965; Carpenter, 1975), yet there has not been a published report on the systemic absorption of this drug from the human eye. It is known, however, that topically applied chloramphenicol is absorbed into the aqueous humour in man (Beasley *et al.*, 1975) and animals (George and Hanna, 1977); systemic absorption of the antibiotic has been detected after topical administration to the eye in animals.

Methods and materials

Five children under 9 years of age, all admitted for routine squint surgery, were given chlorampenicol topically (0·5% chloramphenicol Redidrops) 2-hourly to each eye over a 5 to 7 day period until a dose of between 40 and 52 mg of chloramphenicol had been administered (Table 1). Urine samples were collected within 24 hours of the last dose. These samples were subjected to analysis by gas-liquid chromatography (Least *et al.*, 1977) which with thiamphenicol as internal standard had a lower limit of sensitivity of 1 μg/ml. Polarography was also performed on these samples with a Southern Analytical Davies Diffraction Cathode Ray Oscilloscope. This method was found to be sensitive to levels of chloramphenicol from 0·05 μg/ml upwards when aqueous standards were examined. However, because of non-specific interference from the drug-free urine the practical working limit of the assay proved to be 1 μg/ml.

Results

Table 1 *Patients' age and total dosage of drug applied to both eyes*

Patient	*Age*	*Total dose (mg)*
I	3	48
II	8	52
III	2	47
IV	5	47
V	4	40

These assays failed to detect any chloramphenicol in urine following the dosage schedules outlined. This was the case even when the extraction procedures described above were modified to allow concentration by a factor of 10:1. It thus appears that any chloramphenicol reaching the urine after ocular administration does not attain concentrations exceeding 0·1 μg/ml.

Discussion

The primary excretory pathway for chloramphenicol is via the kidneys; 80 to 90% of an oral dose is eliminated this way within 24 hours of administration (Goodman and Gilman, 1975). If systemic absorption of chloramphenicol is suspected from the eye, one would expect chloramphenicol to appear in the urine in higher concentrations than in the plasma. This effect has been confirmed in animal studies (Conner and Gupta, 1973). It would seem either that systemic absorption directly from the eye into the circulation or via the nasolacrimal duct and through the gastrointestinal tract does not occur in children or that urinary drug levels are below the levels detectable by apparatus at present available.

To reach a total dose of 45 mg a patient would have to use 1 drop of chloramphenicol 3 times daily for 60 days, as 1 drop of 0·5% chloramphenicol is equivalent to 0·05 ml and contains 0·25 mg of chloramphenicol (Parke, Davis & Co., personal communication).

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Two types of bone marrow effects are produced by systemic chloramphenicol administration (Editorial, 1970). Two cases have been reported implicating chloramphenicol eyedrops as the cause of the severe form of bone marrow aplasia. The report by Carpenter (1975) did not provide a definite link between this drug and the aplasia. The aplasia reported by Rosenthal and Blackman (1965), however, may well have been precipitated by chloramphenicol drops, as this patient had a strong family history of fatal aplastic anaemia precipitated by oral chloramphenicol therapy and had used topical drops for an extremely long time, namely, 2 years. In this type of case the possibility of fatal or serious results must be considered, as the likelihood of systemic absorption must be higher than in the shorter periods described above.

Conclusion

Chloramphenicol is a widely used effective topical antibiotic. Even though we were unable to detect systemic absorption of this drug after topical application to both eyes in children over a 5 to 7 day period, the possibility, however remote, still exists that systemic absorption may occur if the drug is used for excessively long periods of time. Ophthalmic practitioners should be alert to this potential hazard and its complications. Further studies to detect systemic absorption of this drug over very long periods, preferably in inflamed eyes, are indicated.

We thank Mr H. H. Fawzi for allowing us to study his patients, and Professor W. S. Foulds and Dr W. Lee for giving advice on the preparation of this paper.

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Systemic absorption of topical and subconjunctival gentamicin

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SUMMARY Ten patients received ocular gentamicin therapy topically or subconjunctivally. Systemic absorption was not detected after topical use but was detected after subconjunctival administration. The relative safety of ocular gentamicin therapy is discussed and the literature is reviewed.

Gentamicin instilled topically as eyedrops or subconjunctivally is commonly used to treat eye infections. It is well known that gentamicin can produce ototoxicity, particularly in patients with renal disease, as this drug is almost entirely excreted by the kidney (Goodman and Gilman, 1975). Previous experiments in man have indicated systemic absorption following subconjunctival use, but the results are conflicting (Furgiuele, 1970; Mathalone and Harden, 1972). We believe this to be the first attempt to evaluate the systemic absorption of gentamicin following both topical and subconjunctival administration.

Patients and methods

Ten patients were divided into two groups. *Group I* consisted of 4 children and 1 adult who had been admitted for routine squint surgery. They were treated with topical gentamicin drops (Genticin 0·3% drops) instilled 2-hourly into both eyes for a 5-day period until between 20 and 38 mg of the drug had been administered (Table 1). Urine was collected over 24 hours after the last dose was administered and analysed for gentamicin by bacteriological (Alcid and Seligman, 1973) and radioimmuno assay (RIA) techniques.

Group II consisted of 5 adult post-cataract patients who were given either 10 or 20 mg of gentamicin subconjunctivally. Blood was removed 1, 2, and 4 to 6 hours after subconjunctival injection. After centrifugation the serum concentration of gentamicin was determined by RIA using a kit supplied by Diagnostic Products Corporation, Los Angeles, Ca 70064, USA. This assay uses ^{125}I gentamicin and had a coefficient of variation in our hands from 10·0% at 0·5 μg/ml to 6·5% at 10 μg/ml. The detection limit of this assay was 0·05 μg/ml when drug-free serum was used to prepare standards.

Table 1 *Total dose of gentamicin applied to both eyes—group I*

Patient	*Age*	*Total dose (mg)*
1	39	27·00
2	8	20·00
3	8	23·00
4	3	38·00
5	3	20·00

Results

Group I. No significant amounts of gentamicin were detected in the urine from any of the 5 patients on topical drops. This applied to the bacteriological method of antibiotic detection, the lower limit of detection being 0·5 μg/ml. With the radioimmuno assay technique non-specific gentamicin binding occurred when urine was used as a control, so that this technique was not applicable to the assay of gentamicin in urine.

Group II. Antibiotic was present in detectable concentration in the serum of all 5 patients tested. Table 2 summarises the serum levels of gentamicin attained in these patients.

Discussion

Gentamicin is very poorly absorbed from the gastrointestinal tract (Goodman and Gilman, 1975), so

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Table 2 *Total dose applied to both eyes with serum concentrations of drug—group II*

Patient no.	*Dose (mg)*	*1 hour (µg/ml)*	*2 hours (µg/ml)*	*4 to 6 hours (µg/ml)*
1	10	0·20	0·20	Nil
2	10	0·20	0·10	Nil
3	10	0·40	0·30	Nil
4	20	0·98	0·76	0·59
5	20	0·58	0·51	0·30

systemic absorption must take place directly into the circulation from the eye. The total doses of gentamicin used in group I patients represent $43\frac{1}{2}$ days of topical therapy had the drug been applied 3 times daily (0·135 to 0·172 mg gentamicin per 0·05-ml drop of Genticin) (personal communication, Nicholas Laboratories). Our inability to detect significant systemic absorption from this group of patients suggests that even in patients with moderate renal impairment long-term low-dose use of gentamicin eyedrops is relatively safe. We were unable to find any reported cases of topical gentamicin eyedrops causing disease of the vestibular apparatus.

Systemic absorption from subconjunctival injection has been confirmed in the patients of group II. We were able to detect significant blood levels 2 hours after injection in all our patients. Although the levels we recorded are higher than those detected by Mathalone and Harden (1972), they are somewhat lower than those reported by Furgiuele (1970). This latter worker detected high plasma levels 4 hours after the initial injection of 10 mg of gentamicin, while we were unable to detect any drug at this time. Data from Case 4 showed gentamicin had a half life ($T\frac{1}{2}$) after subconjunctival administration of 4·2 hours and a total body clearance of 83 ml/min. These figures are comparable to published figures after intramuscular and intravenous injection (Sawchuk *et al.*, 1977) and confirm the reliability of the method we used.

To produce significant ototoxicity gentamicin should reach serum levels of 4 to 5 µg/ml for a period of 7 to 10 days (Mawer *et al.*, 1974). Thus from the results reported in this paper it is clear that gentamicin is a safe antibiotic to use both topically and subconjunctivally. Large subconjunctival doses are unlikely to produce ototoxicity, as the highest dose of plasma gentamicin we could detect was 0·98 µg/ml after a subconjunctival injection of 20 mg.

Conclusion

Gentamicin would be unlikely to produce potentially toxic plasma levels after topical or repeated subconjunctival administration in doses commonly used in ophthalmological practice. This fact is confirmed by the lack of data in the literature connecting ototoxicity with ocularly administered gentamicin. Further studies are indicated to determine how systemic absorption of the drug is affected in the acutely inflamed eye.

We thank Dr Stevenson and Mr Smart for performing the bacteriological assays, Mr H. H. Fawzi and Dr J. L. Jay for allowing us to study their patients, and Professor W. S. Foulds and Dr W. Lee for advice while preparing this paper.

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Lipoid proteinosis (Urbach-Wiethe syndrome)

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SUMMARY A Jewish-Iranian family suffered from lipoid proteinosis. The 8 affected siblings were from consanguineous matings and presented a wide range of phenotypic expressions. Minimal manifestations in 2 heterozygote carriers and the possibility of autosomal recessive inheritance are discussed.

Lipoid proteinosis or Urbach-Wiethe's disease (Urbach and Wiethe, 1929) is a rare hereditary disorder due to a disturbance in the metabolism of lipids and proteins involving the skin and mucous membranes. It starts in early childhood and is characterised by a deposition of plaques on the mucous membranes, an eruption on the face and extensor surfaces of the skin, and nodular formations on the margin of the eyelids (Blodi *et al.*, 1960). The distribution of the lesions, their chronic nature, and their histological picture seem to be pathognomonic.

We here present a family of several individuals with the characteristic features of lipoid proteinosis and analyse the frequency and range of clinical anomalies in order to document the definitive phenotypic spectrum of this condition.

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Family study

Fig. 1 presents the pedigree of a Jewish-Iranian family. The propositus's maternal grandfather (I 2), who was told that he was normal, had 2 children from his first marriage (II 4 and II 5) and 1 child from his second marriage (II 1). The first 2 children married their first cousins (II 3 and II 6) and gave birth to 7 children in each family, with a high rate of affected individuals (III 2, III 4, III 5, III 8, III 10, III 15). The only child from his second marriage (II 1) became the grandfather of 2 other affected nephews (IV 1 and IV 2).

From the 17 examined cases 8 were found to be phenotypically fully affected, while 2 others were

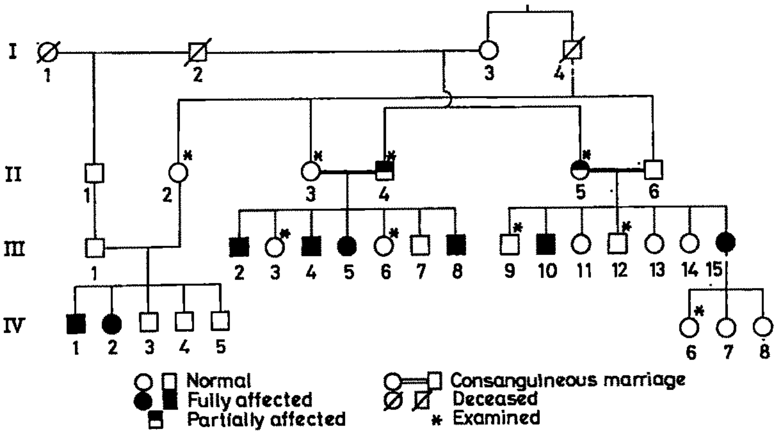

Fig. 1 *Family pedigree*

Table 1 *Summary of anomalies*

			Ocular findings			*Laryngoscopic findings*		*Buccal findings*	
Case no.	*Age*	*Sex*	*Monoliform blepharosis*	*Solitary nodule*	*Dermatological findings*	*With hoarseness*	*Without hoarseness*	*Patchy infiltration*	*Dental abnormalities*
1	19	Male	+	–	+	+	–	+	+
2	32	Female	+	–	+	+	–	+	+
3	50	Female	–	–	–	–	–	–	+
4	3	Male	–	+	–	+	–	+	–
5	11	Male	+	–	+	+	–	+	+
6	13	Male	+	–	+	+	–	+	+
7	21	Male	+	–	+	+	–	+	+
8	48	Male	–	–	–	–	+	–	–
9	15	Male	–	–	–	+	–	+	–
10	9	Female	+	–	+	+	–	+	–

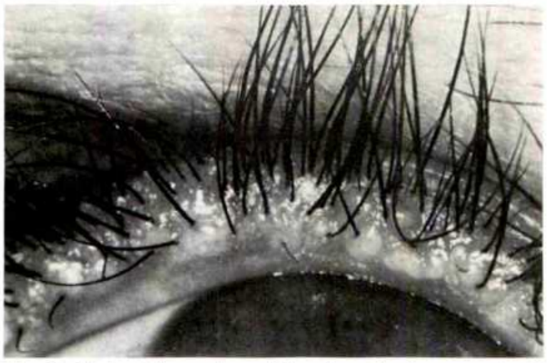

Fig. 2 *Yellowish pearly nodules along the free margin of the eyelid*

considered partially affected. A summary of the anomalies in these 10 cases are tabulated in Table 1 and they are reported below.

CASE 1 (III 10)

The propositus, a 19-year-old man, was referred for an eye examination because of headache. He gave a history of non-progressive hoarseness since early childhood. On ocular examination numerous small yellowish pearly nodules were found along the free margin of both eyelids at and among the roots of the eyelashes (Fig. 2). The lashes grew normally through them, and no trichiasis or loss of cilia was noted. Posteriorly to the nodules, where the change from skin to conjunctiva occurred, a thickened hyalinised line was found. Laryngoscopy revealed a polyp-like irregularity on one of the vocal cords. The posterior wall of the pharynx showed many yellowish patches. The frenulum was indurated, with reduced mobility of the tongue. The entire buccal mucosa was pale, and multiple white-yellowish patches were seen on the inner surface of the lower lip (Fig. 3). The premolar milk teeth of the lower jaw were missing. Multiple varioliform scarrings were found on the skin of the face, on the forehead, cheeks, and chin. The same findings were disclosed on the elbows and knees, together with localised areas of hyperpigmentation. All these scars appeared after a vesicular eruption at the age of 2 years.

CASE 2 (III 15)

A 32-year-old women, the sister of the propositus, had similar lesions on the ocular, oral, and cutaneous areas. The small nodules situated on the margins of all 4 lids were translucent and waxy. Her face had

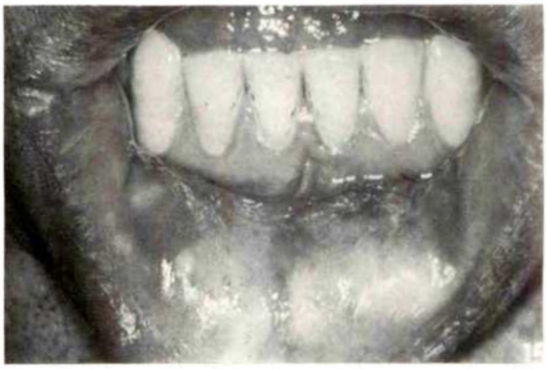

Fig. 3 *White-yellowish patches on the inner surface of the lower lip*

the characteristic pox-marked appearance. Her voice was hoarse owing to the infiltration of the posterior pharynx and buccal mucosa with irregular yellowish plaques. She was the mother of 3 normal girls.

CASE 3 (II 5)
A 50-year-old woman, the mother of the above 2 cases, had no lesions. However, at the age of 30 she lost all her teeth in a short period of time. She knew of no affected relatives in either generation I or II.

CASE 4 (III 2)
A 3-year-old boy was known to have hoarseness from early infancy. Areas of induration of the buccal mucosa and the back of the tongue were found. Along the free margin of each eyelid a solitary pearly nodule was detected. There was no skin involvement at this age. Only after 6 months, when seen again, an impetiginous eruption occurred on the skin of his face and shoulders, leaving, after healing, small punched-out scars. At this time there were already 3 to 4 discrete nodules on the upper lids.

CASE 5 (III 4)
An 11-year-old boy presented the typical picture of the disorder. The clinical manifestations included hoarseness and widely distributed skin changes. In addition to the former cases there was induration of the lips with fissuring of the comissurae. The dentition was abnormal, since the premolar and molar milk teeth of the lower jaw had not erupted.

CASE 6 (III 5)
A 13-year-old girl developed normally until the age of 10 months, when an erythematous, pruritic eruption appeared on her face, elbows, and knees. The eruption healed, leaving pigmented varioliform scars and marked hyperkeratosis on the skin of the elbows and knees. As a young child her voice was hoarse, but it improved in the course of years. The clinical picture was similar to that found in the propositus except for normal laryngoscopic findings. The premolar and molar milk teeth of the lower jaw did erupt, but the teeth remained smaller than usual.

CASE 7 (III 8)
A 21-year-old man presented the full clinical picture of the disease. Multiple discrete and confluent yellowish nodules were among the lashes of both eyelids, and pigmented punched-out scars of different sizes covered his face. He had a roughened skin over his elbows and knees. The tongue was thickened, with loss of papillae, the vocal cords were irregularly indurated, and numerous whitish patches were seen on the buccal mucosa as far as the larynx.

CASE 8 (II 4)
A 48-year-old man, the father of the last 4 cases, had no complaints and appeared normal clinically. Laryngoscopy, however, revealed 2 white small nodules at the posterior third of the vocal cords.

CASE 9 (IV 2)
A 2-year-old boy had a high-pitched hoarse cry when examined. At laryngoscopy a diffuse infiltration of the vocal cords and the buccal mucosa was seen. Neither skin nor eye involvement has yet been found.

CASE 10 (IV 2)
A 9-year-old girl gave a history of hoarseness since the age of 2 years. About the same time she had impetiginous eruptions on her face and elbows. On examination numerous pale yellow-brown scars were seen on her forehead, cheeks, and chin. At the free margin of the superior eyelids 3 to 4 pearly nodules were found (Fig. 4). On the buccal mucosa were scattered small areas of induration. The tongue had reduced mobility.

It is interesting to note that the affected individuals in these families resemble each other more than their own unaffected relatives.

In all the above reported cases biopsy was taken from the skin, buccal mucosa, and palpebral nodules. Histological examination revealed a papillomatous epidermis with a thickened dermis due to hyaline material arranged in homogeneous bundles. The hyaline material stained pale pink with haematoxylin and eosin. In the hyaline areas the nuclei of the fibroblasts and the vascular endothelium were well preserved. A homogeneous eosinophilic hyaline

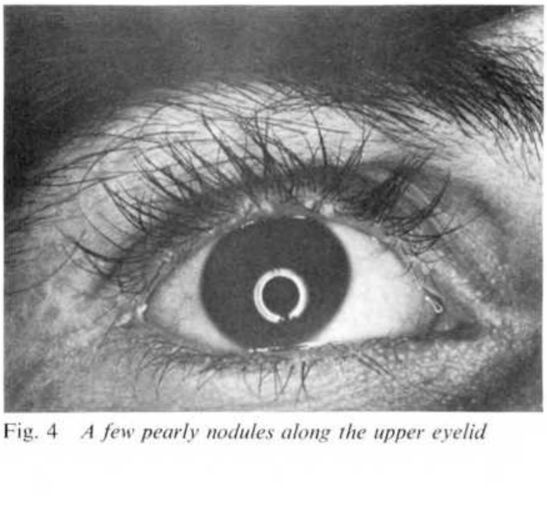

Fig. 4 *A few pearly nodules along the upper eyelid*

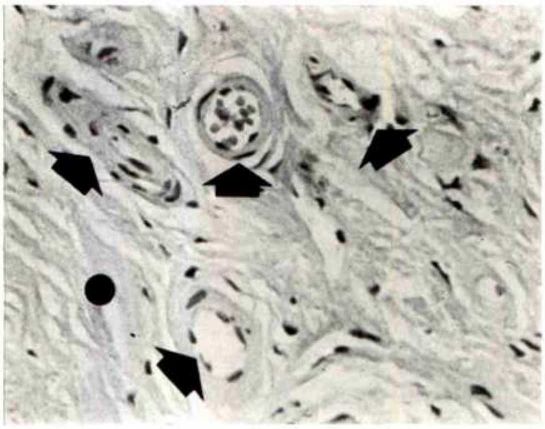

Fig. 5 *The histological changes in the upper dermis. Numerous vessels surrounded by a hyaline mantle (arrows) (Haematoxilin-eosin)*

mantle surrounded the vessels and sweat glands (Fig. 5). A positive reaction to Sudan III staining showed the presence of neutral fats.

Laboratory investigations were carried out in all cases. Values for cholesterol, triglycerides, total lipids, lipoproteins, total proteins, and serum glucose were within normal limits. *X*-ray of the skull and an electroencephalograph showed no abnormalities.

Discussion

The clinical abnormalities in our patients leave no doubt that they are suffering from lipoid proteinosis. Though the expression and degree of organ involvement vary, the total pattern of anomalies is specific enough to support such a diagnosis.

The ocular findings did not cause any symptoms and can be considered almost pathognomonic. Their first appearance was as a solitary pearly nodule at the free margin of the eyelid (case III 2) or as 3 to 4 nodules at the root of the eyelashes (case IV 2). In neither case had the band of hyalinisation at the conjunctival site of the ciliary margin yet appeared. Only in more advanced stages (Cases III 10, III 15, III 4, III 5, III 8) did the papules appear in rows along the margin of the eyelids with the characteristic picture of moniliform blepharosis. Neither conjunctival nor corneal deposits were noted. There was no loss of lashes or trichiasis in any of our cases.

The dermatological picture in lipoid proteinosis is variable, but in our cases 2 clinical findings predominated—multiple varioliform scarrings on the skin of the face, elbows, and knees, and hyperpigmentation in the same areas. These cutaneous changes appeared as a result of vesicular eruptions with long-standing secondary infection in early childhood, followed by pitted scars which became pigmented. The skin lesions were identical in all cases, but their intensities differed in accordance with the age of the patient. The older the patient the more prominent were the lesions.

One of the earliest and commonest clinical symptoms was hoarseness, probably due to the involvement of the mucous membranes of the oral pharynx and incomplete closure of the thickened vocal cords. The oral tissues were infiltrated with yellowish-white patches with the characteristic thickening and limited mobility of the tongue. The faulty dentition found in many of the affected individuals could be explained by the hyalinisation and progressive obstruction of the orifices of Stenson's ducts.

Lipoid proteinosis is a systemic disorder. Besides the skin and mucous membranes it may involve many other viscera (Caplan, 1967) and even the central nervous system (Hewson, 1963). Although the exact aetiology of the disease is unknown, several theories have been put forward to explain its possible mode of origin and pathogenesis. Suggestions that the deposits were protein-bound phospholipids (Urbach and Wiethe, 1929) were followed by theories that the primary defect was a degeneration of elastic and collagen fibres, with release of carbohydrates followed by a secondary deposition of lipid material (Katznelenbogen and Ungar, 1957). Electron microscopic studies (Jensen *et al.*, 1972) pointed to a vascular leakage in the pathogenesis of the disease. The histological picture in our cases shares some features with histiocytosis X, but this pathological similarity does not prove an aetiological identity, and the consistency of the reported cases suggests that they do not represent the same entity.

The pedigree indicates an autosomal recessive inheritance to be the most likely in these families, and this is in accordance with the findings of other investigators (Rosenthal and Duke, 1967, Gordon *et al.*, 1969, Juberg *et al.*, 1975). Though there was parental consanguinity, the parents seemed normal and they had normal and affected offsprings. Moreover, males and females were equally affected, while as far as could be ascertained the relatives of the parents did not display the described anomalies. It may be of interest to note that all previously reported cases of lipoid proteinosis but 1 (Jensen *et al.*, 1972) have been of German extraction, including those found in South Africa (Gordon *et al.*, 1969). Our pedigree is of Jewish-Iranian origin. It is well documented that among the Jewish-Iranian community the rate of consanguinity is as high as 17·5% for first cousins and 26·3% for overall consanguinity (Goldschmidt *et al.*, 1960). As these families originated from the same small village, this high rate of consanguinity adds more evidence to our hypothesis of an autosomal recessive mode of inheritance.

One of the most intriguing questions in diseases with recessive inheritance is whether one can identify the carrier, the heterozygote for the trait, by detecting early signs of the disease. It seems that the laryngoscopic findings in Case III 3 and the premature total loss of dentition in Case III 6 may be considered as microsigns of the heterozygous state. It is obvious, however, that not every heterozygote can be detected phenotypically with certainty.

As it is generally true that most recessively inherited diseases tend to result from enzyme defects (McKusick, 1972), and as this syndrome is due to a metabolic disturbance, an extensive investigation was carried out to find a possible specific biochemical phenotype. But the laboratory results were all normal, being in accordance with previous reports (Muirhead and Jackson, 1963, Jensen *et al.*, 1972; Burnett and Marcy, 1963).

Since the complete clinical syndrome was not delineated until Blodi's report (Blodi *et al.*, 1960), the likelihood is that the prevalence of the ocular involvement in lipoid proteinosis is more widespread than currently appreciated.

The authors acknowledge the kind assistance of Dr Elliot Berry.

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Orbitofacial mucormycosis with unusual pathological features*

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SUMMARY A 52-year-old man with mild diabetes and acute stem cell leukaemia developed an orbitofacial mucormycosis. Cultures showed the fungus to be *Rhizopus oryzae*. Vigorous treatment with amphotericin B and with other bactericidal and bacteriostatic antibiotics for a concurrent sepsis failed to suppress the infections, and the patient died. On post-mortem examination characteristic haematoxylin-staining, broad, aseptate fungal hyphae were found in the right eye, orbit, and lung. A striking and unusual feature of this case is the presence of brightly birefringent crystals within the severely degenerated eye. These were found by histochemical staining and *x*-ray diffraction studies to be calcium salts of fatty acids, apparently liberated from necrotic adipose tissue of the orbit.

Mucormycosis, or phycomycosis, is an infection caused by one of a variety of fungi belonging to the class *Phycomycetes*. Although these fungi are usually saprophytic and ubiquitous in nature, they can cause serious and rapidly fatal infections in man. Usually the patients who manifest this infection have a predisposing debilitating condition, among the most common of which are diabetes with acidosis, diarrhoea and dehydration, renal failure, cirrhosis, leukaemia or other lymphoproliferative disorders, and severe burns. In addition steroids, antibiotics, and cytotoxic agents have been strongly implicated both clinically and experimentally as predisposing agents for this infection. Excellent reviews of this subject are available (Hutter, 1959; McBride *et al.*, 1960; Ferry, 1960; Gass, 1961a; Gass, 1961b; Straatsma *et al.*, 1962; François and Rysselaere, 1972; Schwartz, 1977).

Case report

A 52-year-old white male with acute stem cell leukaemia developed a small, dark, gangrenous-looking lesion in his right superior gingiva. One month prior to this admission he had been admitted to another hospital for evaluation of severe low back pain, the onset of which followed lifting a heavy load. Medical and neurological examinations at that time were within normal limits. Laboratory studies including complete and differential blood count, serum electrolytes, liver function tests, and acid phosphatase were within normal limits. A diagnosis of diabetes mellitus was made on the basis of raised fasting serum glucose and abnormal glucose tolerance test. Radiological examinations at the time of the first admission were within normal limits, with the exception of a possible ruptured lumbar disc. The diabetes was controlled by diet alone, and the patient was discharged on analgesics 1 week after admission.

At the time of the second admission the patient complained of persistent low back pain, loss of appetite, weight loss, and general malaise. Positive findings on physical examination included a palpable spleen, mild abdominal distension, and highly tympanic bowel sounds. A complete blood count revealed haemoglobin of 11·2 g/dl, a white blood count of $22\times10^9/l$ composed almost entirely of blast cells of stem cell or myeloblastic origin, and a platelet count of $98\times10^9/l$. A diagnosis of acute stem cell leukaemia was made. Other laboratory studies and radiological examinations were within normal limits.

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* Read before the Eastern Ophthalmic Pathology Society Meeting, McGill University, Montreal, Quebec, September 1976 (Dr Albert)

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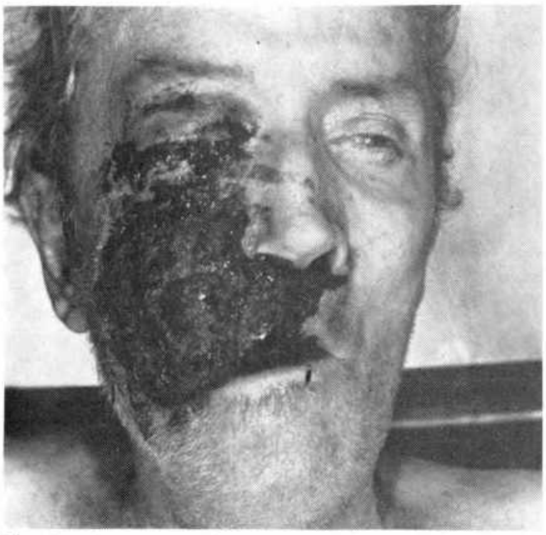

Fig. 1 *Appearance of the patient with right orbitofacial mucormycosis*

The patient was kept in isolation and was followed up with frequent peripheral and bone marrow smears. Treatment with a combination of thioguanine and cytosine arabinoside eventually led to anaplastic marrow and necessitated platelet and white blood cell transfusions.

Three weeks after the second admission the gingival lesion developed; within days it had spread to the cheek and soon involved the entire right side of the face (Fig. 1). Numerous attempts at bacterial culture from this widespread lesion were negative. Biopsy of the lesion showed numerous fungi with broad septate hyphae embedded in a matrix of chronic inflammatory cells and necrotic tissue. A culture of the fungus from the facial lesion was identified as *Rhizopus oryzae*. Treatment with intravenous amphotericin B was begun.

An ophthalmological examination was done about 2 weeks after the development of facial mucormycosis. It showed that vision in the right eye was of no light perception and in the left eye was 6/12 (20/40) with best correction. The right periorbital area was necrotic and indurated. The right eye was proptosed 6 mm, and no extraocular movements could be elicited. Manipulation of the right lids was done with difficulty because of pain and caused some bleeding. The cornea was ulcerated; the conjunctiva of the right eye showed severe injection. The right eye was softer to palpation than the left. On slit-lamp biomicroscopy of the right eye corneal ulceration was evident; the anterior chamber was deep, and no hypopyon was seen. Findings on slit-lamp biomicroscopy of the left eye were within normal limits. The iris, lens, and anterior vitreous body appeared normal on the right. The view of the right fundus was hazy, but no discrete vitreous or retinal lesions were seen. The overall impression was that of a right eye with no light perception owing to a phycomycosis of the right face and orbit. A right cavernous sinus thrombosis was highly suspected. Results of examination of the left eye were within normal limits.

Although treatment with amphotericin B seemed to prevent further extension of the facial lesion, the patient soon developed a partial atelectasis of the right lung, intestinal obstruction, and became septic, with *Escherichia coli* and a *Bacteroides* species being cultured from the blood. Treatment with gentamicin and cephalothin in addition to the amphotericin B did not lead to improvement of the patient's condition. The patient died in septic shock 6 weeks after admission to the hospital and approximately 3 weeks after developing the orbitofacial phycomycosis.

PATHOLOGY

Necropsy revealed a septicaemia, stem cell leukaemia, small bowel perforation with peritonitis and abscess formation, gastric mucosal petechiae, haemorrhagic pyelitis, splenic abscesses, and widespread mucormycosis, with fungi present in the entire right face, orbit, and eye as well as the lung.

Eye pathology (AFIP Accession No. 1546176). The right eye was found to be a necrotic grey-black mass measuring 21 × 27 mm. It had no identifiable external landmarks and did not transilluminate light. The cornea and pupil could not be identified. The optic nerve was 14 mm long and appeared normal. The globe was opened anteroposteriorly. The ciliary body and lens were not distinguishable. The vitreous was replaced by viscid, mottled material. The retina, choroid, and optic disc could not be identified on gross examination. The sclera was largely absent, but where present, was thickened.

Microscopically the right eye was found to be extremely disorganised, with marked degeneration of all layers (Fig. 2). Only small sections of sclera and optic nerve were intact. The remainder of the globe resembled fibrous and fatty tissues with a diffuse infiltration of strongly hematoxylin-staining long, broad, non-septate hyphae, consistent with a fungus belonging to the class *Phycomycetes* (Fig. 3). Within the globe were many crystals which stained intensely with alizarin red (Fig. 4), and were brightly birefringent when observed under polarised light. These crystals did not stain with haematoxylin and eosin, periodic acid-Schiff (PAS), Gromori methenamine silver (GMS), or von Kossa stain. Johnson's 'bubble test' for calcium oxalate was negative

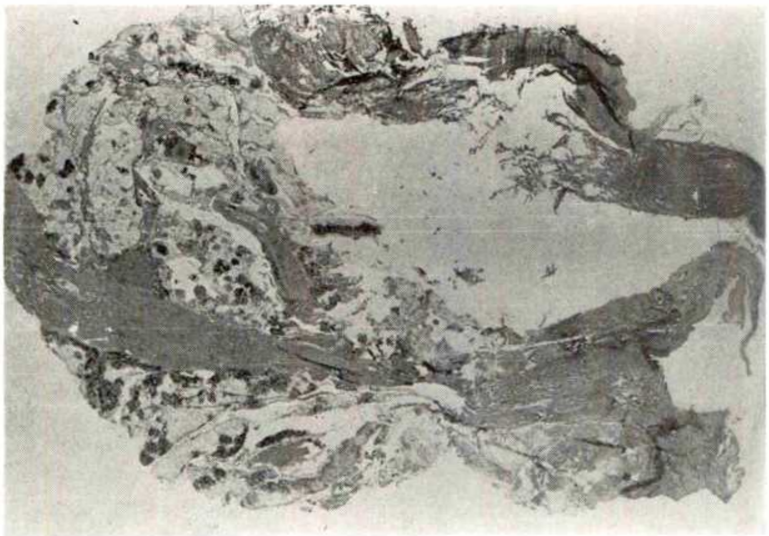

Fig. 2 *Low-power view of right eye, showing extreme destruction (H and E ×3·7)*

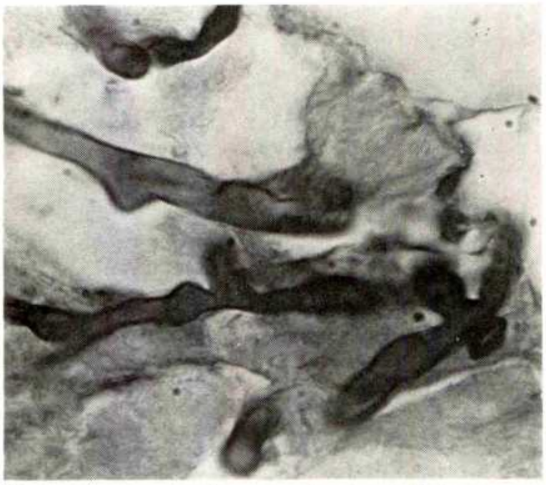

Fig. 3 *Appearance of aseptate fungi typical of* Phycomycetes *(H and E ×410)*

(Johnson, 1956). There were a number of foci of chronic inflammation composed of lymphocytes, plasma cells, macrophages, and scarce eosinophils, interspersed with hyphae. Occasional arterioles could be identified which were completely thrombosed by fungi and debris (Fig. 5). The optic nerve was atrophic and free of fungi. A diagnosis of *Rhizopus oryzae* panophthalmitis with degeneration of the globe and deposition of calcium salts of fatty acids was made.

The patient's left eye was grossly normal but microscopically showed early cataractous changes, peripheral retinal cystoid degeneration with schisis, and questionable early optic atrophy.

Discussion

This patient, like almost all patients who develop mucormycosis, was debilitated before infection. He had diabetes and leukaemia, and was being treated with cytotoxic agents for the latter. Thus there were 3 factors strongly predisposing to subsequent mucormycosis infection. His course was unusual in the fact that, although in most cases an orbitofacial mucormycosis originates in the nasal mucosa or paranasal sinuses, our patient had his infection originate in the gingival mucosa. Further, while

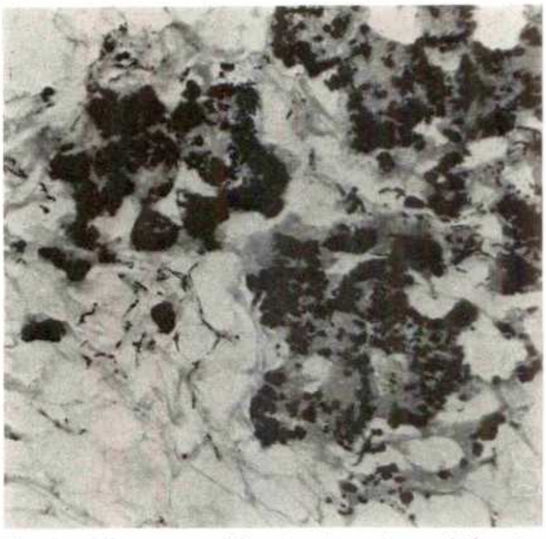

Fig. 4 *Calcium crystal found within right eye (Alizarin red ×400)*

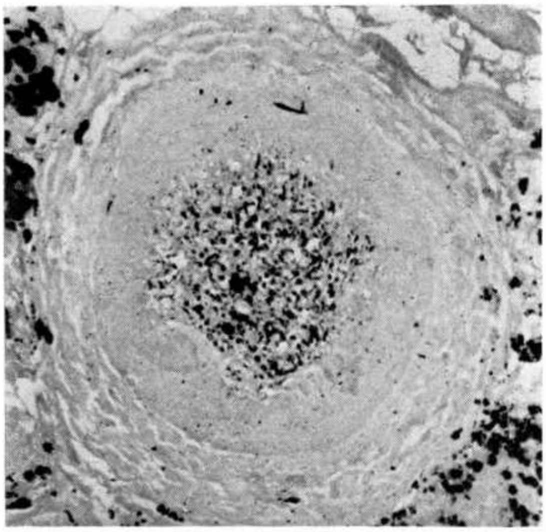

Fig. 5 *Blood vessel thrombosed by fungi and debris, right eye (H and E × 365)*

most cases of orbital mucormycosis go on to involve the meninges and brain, our patient had no clinical or histological evidence of intracranial involvement.

From an ophthalmological viewpoint the most common feature in mucormycosis is an orbital cellulitis. Many cases of this have been reported (Gregory *et al.*, 1943; LeCompte and Meissmer, 1947; Stone, 1950; Martin *et al.*, 1954; Bauer *et al.*, 1955; Harris, 1955; Foushee and Beck, 1956; Johnson, 1956; Baker, 1957; McCall and Strobos, 1957; Bryan *et al.*, 1958; Dwyer and Changus, 1958; Borland, 1959; Burns, 1959; Dolman and Herd, 1959; Faillo *et al.*, 1959; Hutter, 1959; Long and Weiss, 1959; Berk, 1961; Ferry, 1961; Gass, 1961a; Gass, 1961b; Hoagland *et al.*, 1961; Rabin *et al.*, 1961; Wasserman *et al.*, 1961; Bank *et al.*, 1962; Straatsma *et al.*, 1962; Lubbe, 1964; Lincoff *et al.*, 1965; Parmentier *et al.*, 1965; Ginsberg *et al.*, 1966; Tomiyashu and Baker, 1966; Baum, 1967; Blodi *et al.*, 1969; Fleckner and Ginsberg, 1969; Anco and Iriya, 1970; Best *et al.*, 1971; Vergez *et al.*, 1971; Georgiades *et al.*, 1972; Bullock *et al.*, 1974). Intraocular involvement in mucormycosis, diagnosed by the presence of fungi within the globe, is less common but has been reported (Gregory *et al.*, 1943; Martin *et al.*, 1954; Viers and Davis, 1958; Borland, 1959; Smith and Kirchner, 1958; Ferry, 1961; Wasserman *et al.*, 1961; Ginsberg *et al.*, 1966; Tomiyasu and Baker, 1966; Best *et al.*, 1971). From our own experience as well as from a review of the literature this appears to be an extreme case of destruction of the eye by mucormycosis. One possible sequence of events in this diabetic patient may have been severe ketosis on terminal illness with deviation of metabolism to deposit fatty acids with subsequent calcification in this deposit. However, the rapid course which our patient had makes this an unlikely possibility.

It should be noted that 1 week before the patient's death an ophthalmological examination of the affected eye revealed corneal ulceration but an essentially normal anterior chamber, iris, and lens. No lesions of the vitreous and retina were noted. One week later pathological examination of the same eye after the patient's death showed these structures to be completely destroyed and unrecognisable. This demonstrates the rapidity of ocular destruction by this fungus even while the patient was treated by systemic amphotericin B. The question might be raised whether amphotericin B would have been of value in preventing intraocular damage if given intracamerally and intravitreously as well as intravenously.

Of note in the histological findings was the presence of birefringent crystals within the degenerated eye. These crystals were not found elsewhere at necropsy. No similar report of such crystals occurring in a similar case could be found in our review of the literature. Possibly this finding was overlooked in previously reported cases, and we would recommend examining any tissue infected by this fungus with polarised light. Although Wadsworth (1951) mentioned that 'numerous cholesterin crystals' were embedded in a fibrous tissue scar behind the macula in an eye destroyed by mucormycosis, a careful review of his tissue sections by Straatsma *et al.* (1962) revealed that what were initially thought to be fungi within the eye were probably mineralised retinal capillaries.

Finally, it should be noted that the fungi in our patient are seen more easily with haematoxylin than with GMS, the stain usually used to demonstrate fungus. This confirms the previous finding of Straatsma *et al.* (1962) that these fungi had a greater affinity for haematoxylin than for PAS, GMS, or Grindley's stain.

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Immunological activity to different corneal antigens in patients with corneal diseases

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SUMMARY Patients suffering from various corneal diseases and waiting for keratoplasty have been immunologically investigated in order to establish sensitisation to corneal antigens. The presence of lymphocytes sensitised to the soluble fractions from human corneas, bovine corneal epithelium, and bovine corneal stroma, which all possess common antigenicity, could be demonstrated in 30%, 50%, and 23%, respectively, of all patients. In none of these patients could a positive plasma antibody titre to human corneal antigens be detected. The results suggest the dominance of T-lymphocyte activity. No correlation was found between the degree of corneal vascularisation and the presence of sensitised lymphocytes to human corneal antigens. Arrangement of the patients according to diagnosis showed that especially those suffering from herpes simplex virus keratitis reacted positively to human corneal antigens. A possible explanation is given. Lymphocytes of controls showed no or only very low stimulation with the soluble fractions of human corneas or bovine corneal stromas. The soluble fraction of bovine corneal epithelium stimulated the lymphocytes of 6 out of 19 controls. The elimination of the donor corneal epithelium before transplantation may be beneficial in view of the involvement of histocompatibility antigens.

Corneal grafts may be subject to immunological rejection. It is stated that an allograft reaction develops in about 12% of cases with good prognosis (Polack, 1973), which may extend to 65% in patients with preoperatively heavily vascularised corneas (Khodadoust, 1973). The physiological state of the recipient cornea might influence the immune state of the patient.

The role of cellular immunity in corneal grafting has been demonstrated in animal studies by passive transfer of sensitised lymphocytes (Khodadoust and Silverstein, 1976) and by the detection of macrophage migration inhibition factor in the aqueous humour during corneal graft rejection (Sher *et al.*, 1976). This factor has been shown to be an in-vitro correlate of cell-mediated immune reactions (George and Vaughan, 1962; David *et al.*, 1964).

The present investigation has used the lymphocyte stimulation test to estimate the state of presensitisation to corneal antigens in a group of patients awaiting keratoplasty. Furthermore this technique was used to compare the antigenicity of corneal stroma and epithelium to study a possibly beneficial effect of removing the donor corneal epithelium before transplantation.

Materials and methods

SUBJECTS

The investigation included 43 patients suffering from various corneal diseases for at least 6 weeks. All patients were evaluated for keratoplasty. Some patients received topical steroid therapy. Twenty-two healthy volunteers served as controls. Details are given with the results.

ANTIGEN PREPARATIONS

Human corneas, excised from fresh donor eyes, were stored at –70°C until used. All further procedures were carried out at 0–4°C unless indicated otherwise. The corneas were cut in small pieces and homogenised in excess 0·01 M ammonium acetate buffer, pH 7·2, with an Ultra Turrax mixer in a nitrogen atmosphere. Homogenisation was continued by sonication, and the soluble corneal fraction was isolated by centrifugation for 30 minutes at 15 000 *g*. The supernatant was lyophilised, and the product (Hu-CoSo) was stored at –20°C until

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used. Protein content, based on dry weight, was determined according to Lowry *et al.* (1951) and amounted to 50% when bovine serum albumin was used as standard. Corneal epithelium soluble antigens (Bo-EpSo) were isolated from fresh bovine eyes as previously described (Brinkman *et al.*, 1978). After removing epithelium and endothelium the corneal stromas were treated for isolation of the soluble antigens (Bo-SaSo) as described above for Hu-CoSo. The protein content, based on dry weight, of Bo-EpSo and Bo-SaSo amounted to 65%.

LYMPHOCYTE STIMULATION

A sample of heparinised blood was used for plasma preparation and the remainder was diluted with an equal volume of Eagle's minimum essential medium (MEM; Gibco). The mononuclear cells were isolated from the diluted blood by Ficoll-Isopaque centrifugation (Du Bois *et al.*, 1973). Lymphocytes, 3×10^5, were suspended in 1 ml MEM supplemented with 100 units of penicillin and 0·1 mg of streptomycin per ml and 20% heat-inactivated A-rh positive serum. Cultures of lymphocytes were incubated in triplicate with 1 mg Hu-CoSo, 1 mg Bo-EpSo, or 0·5 mg Bo-SaSo (optimal antigen concentrations) for 6–7 days. All antigens had been solubilised in MEM to a concentration of 10 mg/ml and sterilised by sonication. Sterility was checked by incubating the antigens in culture medium. Because some patients were topically treated with corticosteroids (usually dexamethasone), the stimulation activity of the lymphocytes was controlled by incubation with 5 μg phytohaemagglutinin-P (Difco) for 3 days. Control cultures contained neither antigen nor mitogen. Twenty-four hours before harvesting 0·5 μCi tritiated thymidine (specific activity 25 curie/millimole) was added. Harvesting of the cells was done by filtration under reduced pressure through Millipore glass fibre filters. The filters were incubated in 0·5 ml Nuclear Chicago Solubiliser (NCS), diluted 1 to 3 with toluene-based scintillation fluid containing 100 mg di-methyl-POPOP (2,2′-p-phenylen-bis-(5-phenyloxazol)) and 5 g PPO (2,5-diphenyloxazol) per litre, for 30 minutes at 20°C. After addition of 9·5 ml scintillation fluid, containing 1 ml/l glacial acetic acid, the activity was counted in a liquid scintillation counter. The degree of stimulation is reported as the stimulation index (SI), which is expressed as: SI=mean counts per minute (c.p.m.) of cultures in the presence of antigen/mean c.p.m. of cultures in the absence of antigen.

An $SI\geqslant2$ with Hu-CoSo and an $SI\geqslant3$ with Bo-EpSo or Bo-SaSo was considered to be positive.

ANTIBODY TITRE

The plasma antibody titre was estimated by the haemagglutination test (Herbert, 1973). 1 ml 2% (v/v) tanned sheep erythrocytes was incubated with 1 mg Hu-CoSo.

IMMUNODIFFUSION

Immunodiffusion was performed in 1% agarose in 0·1 M Tris-Veronal buffer, pH 8·8. Bo-EpSo and Bo-SaSo were solubilised in saline to a concentration of 10 mg/ml and 20 mg/ml respectively. In order to absorb antibodies to serum proteins the central well was filled with bovine serum and incubated for for 1 hour at 37°C before applying the anti-total human cornea antiserum. This antiserum was prepared by injecting rabbits subcutaneously at multiple sites in the back with 5 mg human corneal antigens (protein based) solubilised in 1 ml phosphate buffered saline (PBS), pH 7·4, and emulsified with 1 ml Freund's complete adjuvant. Boosting was performed 4 and 6 weeks later with 5 mg human corneal antigens solubilised in 1 ml PBS. One week after the last injection the rabbits were bled.

Results

LYMPHOCYTE STIMULATION

A stimulation index of 10 or more was found after incubating the lymphocytes of patients and controls with PHA-P. This suggests that, despite the fact that some patients received corticosteroid therapy, their lymphocytes still possessed the potentiality to be stimulated. The stimulation activity of the different corneal antigen fractions on the lymphocytes of the patients with corneal disease and the healthy persons is shown in Fig. 1. A significant difference (Mann—Whitney U-test) was found between the stimulation indices of the patients with corneal disease and the healthy subjects after incubation of their lymphocytes with human corneal antigens ($P<0·002$). No significant difference could be observed between both groups of subjects when tested with bovine corneal stroma antigens or bovine corneal epithelium antigens ($P>0·09$, for both antigen fractions). The relation between the diagnosis of the patients and the presence of sensitised lymphocytes is also demonstrated in Fig. 1.

In comparison with control subjects patients suffering from keratitis caused by herpes simplex virus (HSV) infection showed a statistically highly significant difference in stimulation activity after incubation of their lymphocytes with human corneal antigens ($P<0·001$). No difference was found with bovine corneal epithelium antigens ($P>0·06$) and bovine corneal stroma antigens ($P>0·06$). The lymphocytes of patients suffering from bullous keratopathy also reacted clearly positively with human corneal antigens ($P<0·005$). With bovine corneal epithelium and bovine corneal stroma antigens no statistically significant difference between these patients and healthy subjects could be detected ($P>0{\cdot}1$, for both antigen fractions). Patients suffering from keratoconus (1), scrofulosa (1), herpex zoster virus keratitis (1), Fuchs's dystrophy (1), pterygium (1), Peters's anomaly (2), physically or chemically induced keratitis (7), or idiopathic stromal keratitis (3) (classification according to Moore and Aronson, 1971) showed no statistically significant difference in lymphocyte activation with either antigen as compared to controls ($P>0{\cdot}05$ for each antigen).

An SI $\geqslant 2$ with human corneal antigens and an SI$\geqslant 3$ with bovine corneal antigens being considered a positive lymphocyte response, lymphocytes sensitised to the soluble fractions from human corneas, bovine corneal epithelium, and bovine corneal stroma could be demonstrated in 30%, 50%, and 23% respectively of all patients. According to this criterion significant differences (Fisher's one-sided exact test) in lymphocyte activity with human corneal antigens ($P<0{\cdot}0005$) and bovine corneal stroma antigens ($P<0{\cdot}05$) were found only between patients suffering from herpes simplex virus keratitis and healthy persons, as shown in Table 1. Six control subjects (31%) reacted positively with bovine corneal epithelium antigens.

Corneal vascularisation might influence the state of immunity of patients. However, as shown in Table 2, no relation could be detected between the degree of corneal vascularisation and the presence of lymphocytes sensitised (i.e., SI $\geqslant 2$) to human corneal antigens. Of 25 patients with heavily or mildly vascularised corneas 6 (24%) reacted positively with human corneal antigens. The patients with avascular corneas reacted in 7 (39%) of the 18 cases positively with this antigen fraction.

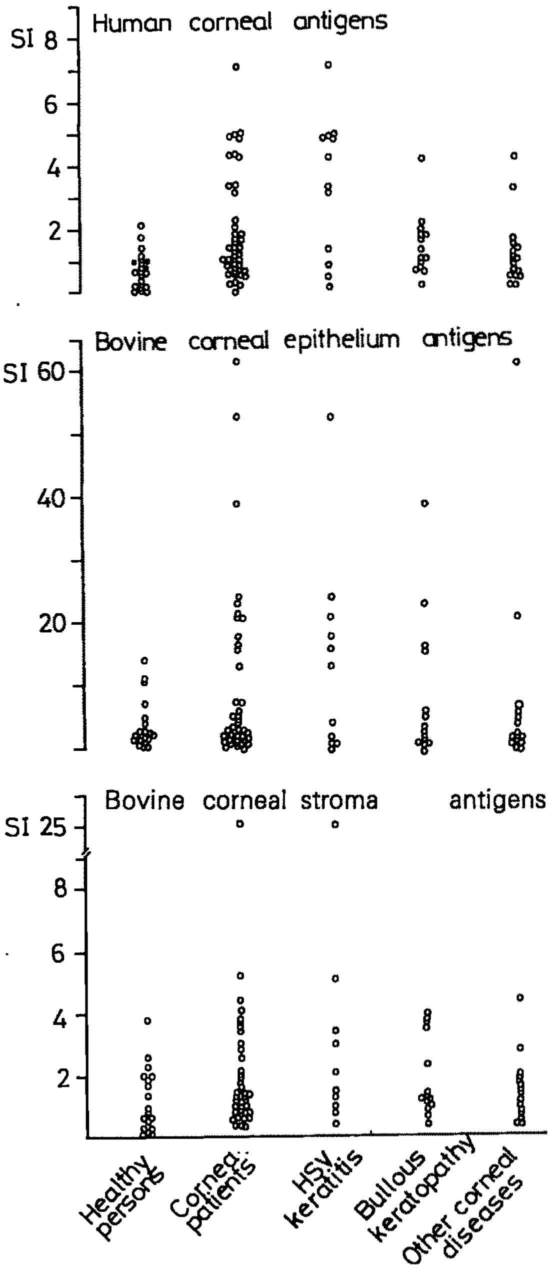

Fig. 1 *Stimulation of lymphocytes of healthy subjects and patients with corneal disease with human corneal antigens, bovine corneal epithelium antigens, and bovine corneal stroma antigens expressed as stimulation index (SI). The results of the patients suffering from HSV keratitis, bullous keratopathy, and other corneal diseases have been taken together in the group indicated as cornea patients.*

Table 1 *Stimulation of lymphocytes of patients, suffering from corneal diseases and of healthy persons by Hu-CoSo, Bo-EpSo and Bo-SaSo*

Diagnosis	*Number of total subjects (with percentage) with positive SI to*		
	Hu-CoSo	*Bo-EpSo*	*Bo-SaSo*
Bullous keratopathy	3/14 (21%)	7/14 (50%)	4/14 (29%)
Herpes simplex virus keratitis	8/12 (67%)*	7/11 (64%)	4/10 (40%)*
Other corneal diseases**	2/17 (12%)	6/15 (40%)	1/15 (7%)
Healthy***	1/22 (5%)	6/19 (32%)	1/18 (6%)

*Significant at $P<0{\cdot}05$ (Fisher's one-sided exact test). ***Eighteen healthy subjects were tested with Bo-SaSo, 19 with Bo-EpSo, and 22 with Hu-CoSo. **See text (Results).

Table 2 *Relation between corneal vascularisation and lymphocyte stimulation with Hu-CoSo*

Degree of vascularisation	*Stimulation index*	
	Positive	*Negative*
Heavy	4/13 (31)*	9/13 (69)
Mild	2/12 (17)	10/12 (83)
No	7/18 (39)	11/18 (61)

*Number of total patients (with percentage).

ANTIBODY TITRE

The plasma antibody titre to human corneal antigens of all patients and controls was zero.

IMMUNODIFFUSION

Fig. 2 shows the formation of 1 precipitin line between rabbit antihuman cornea antiserum and Bo-EpSo and 2 precipitin lines between rabbit antihuman corneal antiserum and Bo-SaSo. With bovine serum no precipitin line was found.

Discussion

Sensitisation of animals by tissue transplantation or antigen injection followed by keratoplasty leads to enhancement of the rejection of the corneal graft (Maumenee, 1951; Payrau, 1966; Treffers and Broekhuyse, 1977). Corneal graft rejection may be partly related to cell-mediated immunity (Polack, 1972; Khodadoust and Silverstein, 1976; Sher *et al.*, 1976), which may be detected by the lymphocyte stimulation test (Fleer *et al.*, 1976). Our results are consistent with this hypothesis by showing the presence of corneal antigen sensitised lymphocytes in the blood of patients suffering from corneal diseases. The observed difference in lymphocyte responses due to different corneal antigens suggests some kind of antigen specificity of this immune activity.

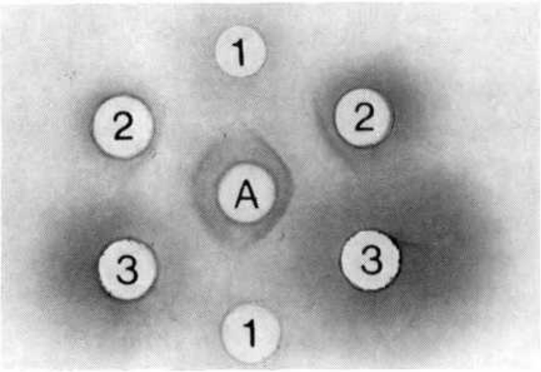

Fig. 2 *Immunodiffusion of antihuman corneal antiserum* (A) *versus bovine serum* (1), *bovine corneal stroma antigens* (2), *and bovine corneal epithelium antigens* (3). *The central well was prefilled with bovine serum for 1 hour at 37°C in order to absorb antiserum protein antibodies*

The use of bovine corneal epithelium antigens and bovine corneal stroma antigens for investigation of a possible sensitisation of human beings to these antigens has been partly justified by immunodiffusion. Clear precipitin lines could be detected between antihuman corneal antiserum and the soluble antigens of these bovine tissues, indicating the presence of common antigenic determinants. The relatively high percentage of the controls reacting positively with the soluble antigens from bovine corneal epithelium as compared to stroma is a drawback and may be due to histoincompatibility. Incubation of human lymphocytes with these antigens may lead to a stimulation by histocompatibility antigens (or soluble precursors), probably more being present in the soluble fraction of the epithelium than in the soluble fraction of the stroma. The results described in this report may therefore suggest that separation of the epithelium from the donor cornea before keratoplasty eliminates most of the histocompatibility antigens and consequently might increase the chance of success.

Arrangement of the patients into groups according to the diagnosis of the corneal disease showed that bullous keratopathy sometimes caused an increased lymphocyte stimulation. The oedematous state of the cornea might result in a loss and alteration of corneal antigens in these patients, which might explain this increased response to human corneal antigens as compared to that of controls. Further evaluation of the results shows that especially those patients suffering from herpes simplex virus keratitis reacted positively with human corneal antigens. This group of patients appeared also to be more sensitised to bovine corneal epithelium and bovine corneal stroma antigens than the other groups of patients (Fig. 1). For bovine corneal epithelium antigens, however, this difference was statistically significant only at the $P=0 \cdot 1$ level.

Several explanations are possible for the high number of herpes simplex virus keratitis patients showing lymphocyte stimulation. The intense vascularisation of the cornea often encountered in this type of patients might create the possibility of lymphocytes coming into contact with corneal antigens. However, the influence of another or additional factor is indicated by the absence of a correlation between corneal vascularisation and a positive lymphocyte response (Table 2). This is

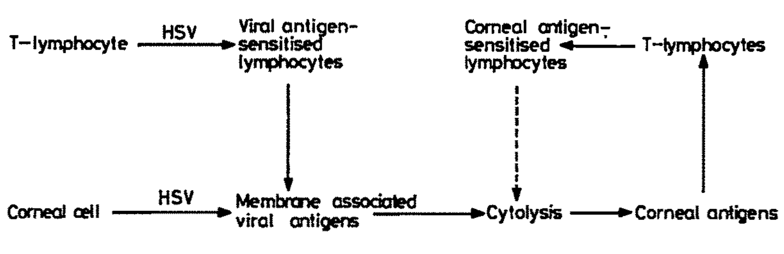
T-lymphocyte
HSV
Viral antigen-sensitised lymphocytes
Corneal antigen-sensitised lymphocytes
T-lymphocytes
Corneal cell
HSV
Membrane associated viral antigens
Cytolysis
Corneal antigens

Fig. 3 *Corneal cells exposing membrane associated viral antigens are recognised by peripheral viral antigen-sensitised lymphocytes. The consequent cytolysis results in release of corneal specific antigens which activate the immune system of the patient. This is measured by the in-vitro lymphocyte stimulation*

supported by the fact that corneal vascularisation is also seen in other forms of keratitis without eliciting an immune response. It is likely that the change of cell-surface antigens of corneal cells by incorporation of viral antigens, demonstrated after infection of the cornea with the herpes simplex virus (Henson *et al.*, 1974; Metcalf and Helmsen, 1977), might be one of the primary causes of the immune response. Cell-mediated immune activity to viral antigens has been demonstrated after herpes simplex virus infection in animals (Swyers *et al.*, 1967; Metcalf and Kaufman, 1976) and in man (Russell *et al.*, 1976). A second contact between systemic sensitised lymphocytes and viral antigens present on the corneal cell surfaces may lead to corneal opacification, probably by destruction of the corneal cells by direct contact or by the release of cytolytic lymphokines. The consequent liberation of soluble corneal specific antigens together with high vascularisation might explain the large number of patients with herpes simplex virus keratitis who are sensitive to corneal antigens, resulting in poor prognosis for successful keratoplasty. This hypothesis is illustrated in Fig. 3. The absence of detectable plasma antibodies to human corneal soluble antigens suggests also in this particular case that especially T-lymphocytes are responsible for this immune activity.

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An unusual organism causing orbital cellulitis

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SUMMARY Bacterial orbital cellulitis is a feared complication of paranasal sinus infection. Staphylococcus and Streptococcus species are the commoner pathogens involved in these cases. However, anaerobic bacteria and unusual Gram-negative organisms should be suspected as well. We treated a case of bacterial orbital cellulitis due to foci of infected paranasal sinuses caused by *Eikenella corrodens*, a Gram-negative rod. The patient was managed with intensive antibiotic coverage and surgical intervention.

Bacterial orbital cellulitis may endanger sight as well as life. Its primary cause is an extension of pathogens from infected paranasal sinuses (Smith and Spencer, 1948; Haynes and Carmblett, 1967; Jarret and Gutman, 1969; Chandler *et al.*, 1970). Thus, the organisms commonly responsible for sinus infection, *Staphylococcus aureus* and *Streptococcus* species, are the most common aetiological agents involved in orbital cellulitis (Haynes *et al.*, 1967; Jarret *et al.*, 1969). Treatment is based on intensive antibiotic therapy with adjunctive surgical intervention. This report describes a case of orbital cellulitis caused by an unusual bacterial organism that was successfully treated in that way.

Case report

A 19-year-old white man was referred to the University of Illinois Eye and Ear Infirmary after a 2-day history of progressive pain, swelling, and redness of his left upper and lower eye lids. The patient had sought medical attention the day before admission, and had received 300 mg clindamycin phosphate intramuscularly. The patient reported a 5-year history of intermittent sinus infections that had been treated with oral ampicillin sulphate. Two weeks before the onset of the present symptoms the patient had used ampicillin sulphate for a cold-like illness characterised by running nose and low fever. He denied trauma or previous ocular surgery.

Physical examination at the time of admission revealed severe swelling of the left upper and lower eyelids with marked induration and erythema. A sharp demarcation line was noted in the left upper eyelid between erythematous and non-erythematous tissue. Marked proptosis was present. The best corrected visual acuity was 20/20 OD and 20/40 OS. The right eye was unaffected. The conjunctiva of the left eye displayed 3+ injection, with chemosis. The cornea, anterior chamber, and pupillary response were normal. Severe limitation of motility was observed. The fundus was normal.

Crepitation of the left ethmoidal area was found. The remainder of the physical examination was within normal limits.

Sinus *x*-ray films obtained on admission (Fig. 1) showed clouding of the ethmoid and maxillary sinuses. A Gram stain of nasal secretion revealed no organisms. The leukocyte count was 10 500/mm^3 (10·5 $\times 10^9$/l) with a marked left shift. The patient was started on a regimen of intravenous methicillin sodium, 2 g every 4 hours, which was alternated with 3 million units of intravenous penicillin every 4 hours. Twelve hours after admission his condition had not improved, and an external and internal ethmoidectomy and maxillary antrostomy were performed.

A curved incision 4 cm long was made above the medial canthus, laterally along the nasal bridge, and extended to the supraorbital rim below the level of the eyebrow. The incision was carried through the periosteum to the bone. The periosteum was raised to expose the area of the orbital plate of the frontal bone. With a feeler elevator the eroded medial orbital wall was entered, and approximately 10 ml of pus was aspirated and taken for Gram stain and anaerobic cultures. An intranasal ethmoidal ap-

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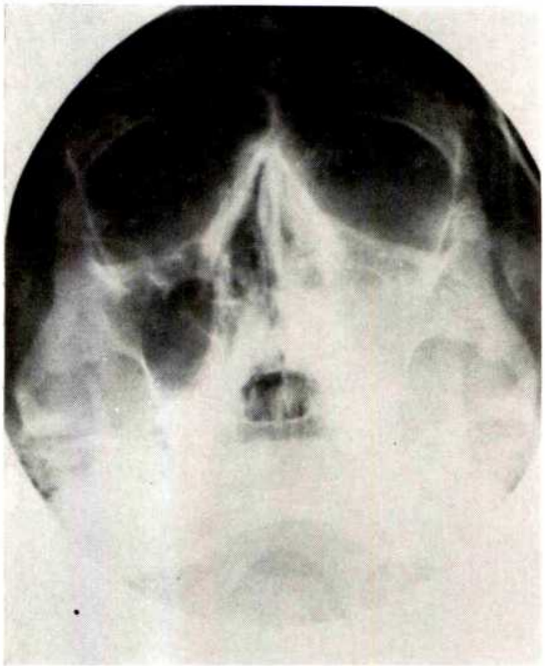

Fig. 1 *Sinus x-ray film taken at admission reveals diffuse soft tissue swelling in region of left cheek and clouding of ethmoid and maxillary sinuses*

proach was then performed lateral to the middle turbinate.

When the medial ethmoid cells were opened, additional pus was aspirated. Finally, by placing a small trocar beneath the left inferior turbinate, an intranasal antrostomy was done and the maxillary antrum was entered. A small rubber drain was sutured into place to drain the maxillary antrum. The external incision was loosely closed in layers with a 1-cm rubber drain placed in position.

A Gram stain of the aspirated material disclosed predominantly Gram-positive cocci suggestive of *Streptococcus,* although *Staphylococcus* could not be ruled out. No Gram-negative organisms were seen. The patient was continued on the same preoperative antibiotic regimen. On the third postoperative day the organism was characterised.

The organism, which was isolated on blood agar and isovitalex-enriched chocolate agar, grew so slowly that in 72 hours the dry colonies were only 0·5 mm or less in diameter. Within 5 to 7 days typical growth of pitting colonies appeared. Gram stains from culture plates done at 72 hours revealed a thin Gram-negative rod, $0{\cdot}5\times1{\cdot}5$ μm. Biochemical analyses showed the organism to be positive for lysine, ornithine, oxidase, and nitrate, and negative for arginine, catalase, and indole. It did not ferment carbohydrates. In disc antibiotic susceptibility studies the organism was seen to be susceptible to ampicillin, cephalothin, tetracycline, penicillin, and erythromycin, and resistant to oxacillin and clindamycin. From these studies the organism was classified as *Eikenella corrodens* (Hill *et al.*, 1970). *Staphylococcus epidermidis* was also isolated.

On the basis of the antibiotic sensitivity studies the patient was given 4 million units of intravenous penicillin every 6 hours, and the methicillin sodium was discontinued. By the fourth postoperative day he had regained full motility. No evidence of proptosis or conjunctival chemosis was noted. Minimal eyelid oedema persisted, but was not visible after 2 weeks of antibiotic therapy, after which the patient was discharged.

Discussion

Eikenella corrodens, a facultive Gram-negative rod, has only recently been implicated as a human pathogen. To our knowledge this organism has never been isolated from ocular tissue, though it has been reported from numerous and diverse clinical sources (Zinner *et al.*, 1973).

This organism has been isolated in 16 of 64 positive blood cultures from 100 patients taken 1 minute after tooth extraction (Khairat, 1967). In a series of 6 children it was detected in subdural empyema and brain abscess secondary to frontal sinus infection (Marsden and Hyde, 1971). Additional infections noted in the latter series included abdominal abscess, otitis media, and a reaction from a human bite. The organism was isolated in pure culture in 17 cases of infected frontal sinuses, wounds, and peritoneal fluid, and in mixed flora from abscesses and sputum (Bottone *et al.*, 1973).

The most recent report describes 7 of 10 cases in which *Eikenella corrodens* was isolated in pure culture from abdominal abscess, lung empyema, meningitis, and endocarditis (Dorff *et al.*, 1974). It appears to reside in the oropharynx and the gastrointestinal tract. The paranasal sinuses may become involved if chronic infection is left untreated.

Our patient developed orbital cellulitis from a focus of chronic paranasal sinus infection. Although Gram stain of material obtained intraoperatively suggested *Staphylococcus* or *Streptococcus*, cultures grew only *Staphylococcus epidemidis* as a contaminant. No suspicion of Gram-negative infection was present until the culture results were available. Since this case was seen an additional case of orbital cellulitis caused by *Eikenella corrodens* has been observed at our institution. This case was due to an infected orbital prosthesis in a patient who had undergone orbital exteneration.

When investigating organisms causing orbital cellulitis as a result of chronically infected sinuses anaerobic bacteria and unusual Gram-negative pathogens as well as the more common bacterial agents must be considered. We recommend the use of a broad spectrum of antibiotics such as gentamycin and penicillin or methicillin and penicillin until definite culture results are received, for some organisms may not be identified until after a long (3-day) incubation.

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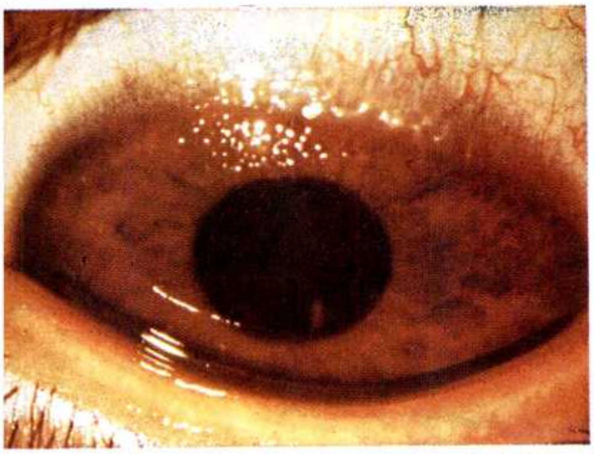
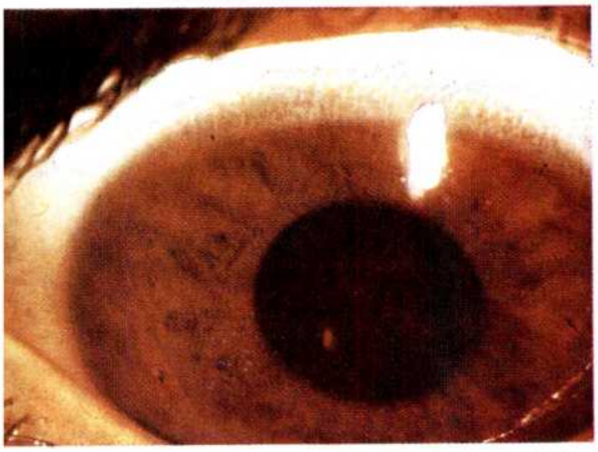


The superior limbus in a placebo treated eye of a patient suffering from rnal kerato-conjunctivitis, stained with fluorescein. Note the limbal peraemia and swelling and the irregularity of the corneal surface.



. The opposite eye of the same patient treated with sodium cromoglycate ye drops. Before treatment, both eyes appeared similar.

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British Journal of Ophthalmology, 1979, **63**, 713–717

Ophthalmological features of Aicardi's syndrome: report of two cases

E. E. LIMNAIOS, C. P. PANAYIOTOPOULOS, G. THEODOSIADIS, M. ECONOMOU, AND T. PAPAPETROPOULOS

From the Department of Neurology, Division of Neuro-ophthalmology, University of Athens, Athens, Greece

SUMMARY Two Greek female patients with Aicardi's syndrome are presented. The clinical picture, electroencephalogram, computer axial tomography scan, and the ophthalmological findings in these patients are described. The ocular features are emphasised because they can establish the diagnosis of this rare syndrome.

In 1965 Aicardi, Lefebvre, and Lerique-Koechlin described in a brief report a new syndrome consisting mainly of spasms in flexion, agenesis of the corpus' callosum, and ocular anomalies (Aicardi *et al.*, 1965). This clinical entity is now known as Aicardi's syndrome and from various reports it seems to have the following characteristics. Clinical manifestations include infantile spasms. Only females are attacked. Mental retardation occurs. Pneumoencephalography or computer axial tomography (CT-scan) shows agenesis of the corpus callosum. The EEG shows hypsarrhythmia and asynchronous activity of the 2 hemispheres (Fariello *et al.*, 1977). There are skeletal anomalies such as scoliosis, fusion of the vertebral bodies, and hemivertebrae. Ocular features include choroidoretinal 'lacunae' and more rarely colobomas of the optic disc, persistent pupillary membrane, staphylomas, proliferation of glial tissue at the optic disc, and microphthalmia.

Histopathological studies have shown absence of the pineal gland in addition to agenesis of the corpus callosum (de Jong *et al.*, 1976). As regards the intraocular anomalies, the main interest has been focused on the chorioretinal lacunae. They have been found after fluorescein angiography as fluorescein-negative areas, suggesting choroidal atrophy (Hammami *et al.*, 1972). Detailed histological examination has shown that at the lacunae the retina is normal, the pigment epithelium is depigmented but intact, and the choroid has gross atrophy (Bary, 1973; de Jong *et al.*, 1976).

The ocular and central nervous system abnormalities are thought to occur between the 4th and 7th week of intrauterine life. The retinal pigment epithelium appears in the 4th week, the choroidal pigment appears in the 5th week, and the commissural plate is formed from the 4th to the 7th week, although the full development of the corpus callosum takes up to the 3rd month of fetal life to be completed (Andreu, 1973). The various defects we often see in this area can be explained by the long time taken for the midline structures of the brain to be formed (Saraux *et al.*, 1969).

The absolute restriction of the syndrome to the female sex was by Aicardi *et al.* (1965) to the presence of a single dominant gene on the X chromosome, which is produced by a spontaneous mutation and is lethal to the male. On the other hand de Jong *et al.* (1976), after reporting no evidence of pineal gland in 2 patients with Aicardi's syndrome and regarding this gland as an important biological clock for sexual development, believe that the absence of the gland is incompatible with the development of a viable male child regardless of the cause of the syndrome.

The prime criteria for the diagnosis of Aicardi's syndrome are infantile spasms, agenesis of the corpus callosum, and chorioretinal 'lacunae.' With these criteria some 78 cases of the syndrome in children have been reported from various parts of the world. We report on the first 2 cases found in Greece.

Case reports

CASE 1

The patient was a girl aged 25 months. She was born at term to 2 healthy parents; the mother was 30 and the father was 35 years old. There was also a healthy son of 9 years in the family. No family history of ocular or neurological disorders was reported.

Correspondence to Dr E. E. Limnaios, Aiginition Hospital, Athens, Greece.

The patient did well until the 4th month of her life. Then she began to have tonic spasms of the trunk and both upper and lower limbs, with synchronous turning of the head and eyes to the left. Each episode lasted for a few seconds. The frequency of the attacks was 3 to 5 per day.

On examination she had a right hemiparesis. She responded well to photic stimuli. Ocular motility and optokinetic responses were normal. A rough evaluation of visual fields by using familiar toys and lights of various colours showed no gross field defects. The pupillary reaction to light and near vision was also normal. Examination of the anterior segment gave no abnormal findings. In the right fundus the optic disc was normal, with an excess of black pigment round it. Close to the optic disc and at the 1 and 11 o'clock positions we found 2 well defined chorioretinal lesions of white-yellow colour with some pigment at their border. Below the optic disc and at the 4 o'clock position an area of deeper pigmentation was seen. The blood vessels passed over the lesions without interruption (Fig. 1). In the left fundus the optic disc was also normal. Pale yellow lesions of less than 0·1 disc diameter were seen round the posterior pole.

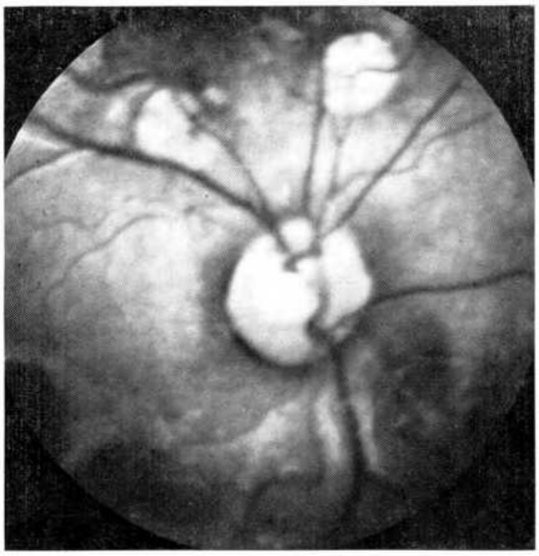

Fig. 1 *Case 1. Large chorioretinal 'lacunae' in the right fundus*

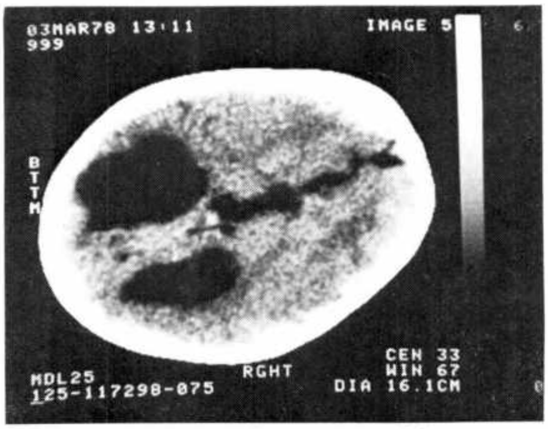

Fig. 3 *Case 1. CT-scan shows agenesis of the corpus callosum and ectopic parenchyma in the left lateral ventricle*

The EEG showed hypsarrhythmia, which was markedly asynchronous and more pronounced in the left hemisphere (Fig. 2). The CT-scan showed agenesis of the corpus callosum and ectopic parenchyma in the left lateral ventricle (Fig. 3). Laboratory tests for venereal disease and Reiter's syndrome were all negative.

The patient was treated with ACTH, nitrazepam, phenobarbitone, and sodium valproate. The EEG

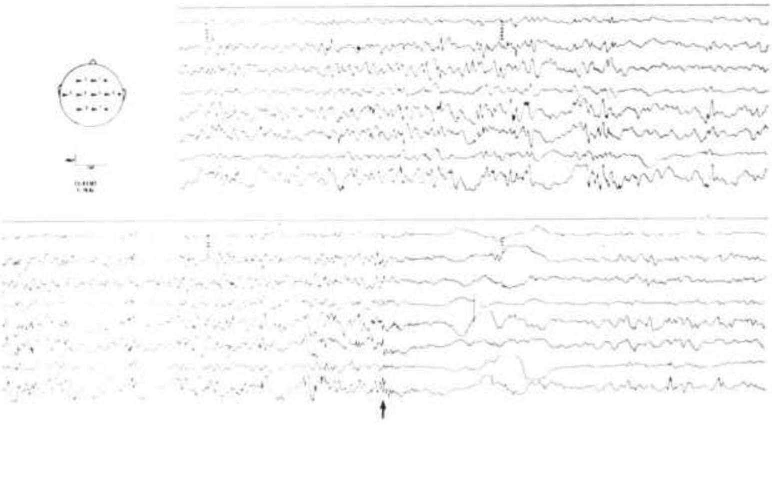

Fig. 2 *Case 1. EEG recorded at the age of 6 months. Gross abnormalities mainly on the left. At the arrow the patient had a flexion spasm*

improved and the epileptic fits were reduced to 1 per week. She had still a moderate right hemiparesis and developed mild mental retardation.

CASE 2

The patient was a girl 6 months old. She was the first and only child of healthy parents, the mother being aged 32 and the father 36. She was born at term after a normal pregnancy. There was no family history of ocular or neurological disease.

In the fourth month of her life she began to have tonic spasms of the upper and lower limbs, flexing them and turning the head and eyes to the right. An estimated number of 50 spasms were seen on each attack, and the whole episode lasted for a few seconds, to be repeated about 8 times every day.

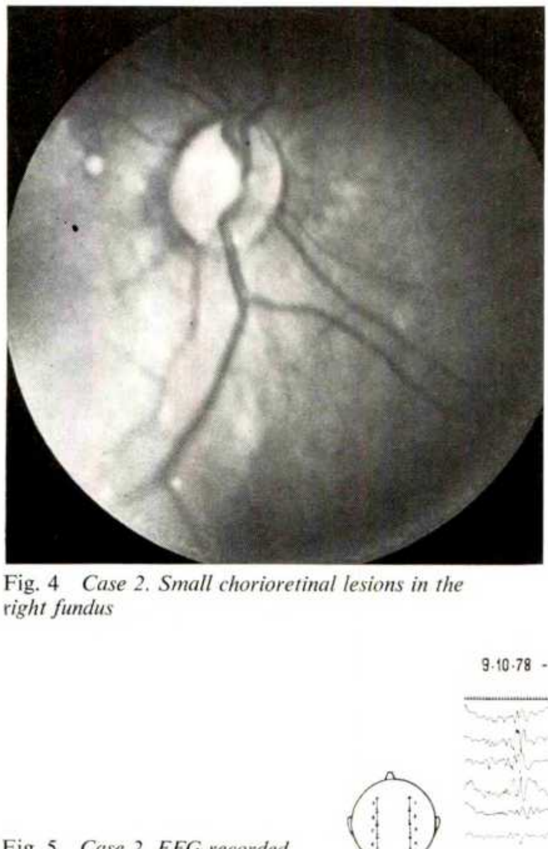

Fig. 4 *Case 2. Small chorioretinal lesions in the right fundus*

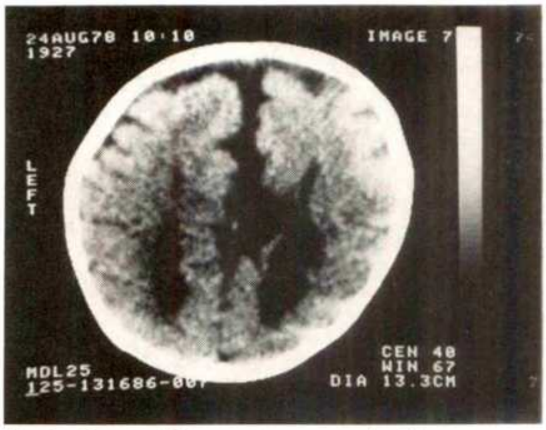

Fig. 6 *Case 2. CT-scan shows agenesis of the corpus callosum*

On examination she was found to have a right hemiparesis. She responded well to photic stimuli. The ocular motility and optokinetic responses were normal. The pupils were equal and responded well to light. The structures of the anterior segment were normal and the vitreous was clear. The optic discs and the central retinal vessels were also normal. In the posterior pole of both eyes small, round, pale yellow lesions were seen, of less than 0·1 disc diameter. Deeper pigmentation was seen at the border of each lesion (Fig. 4).

The EEG showed hypsarrhythmia and was markedly asynchronous (Fig. 5). The CT-scan was typical of agenesis of the corpus callosum (Fig. 6). Laboratory investigations were negative.

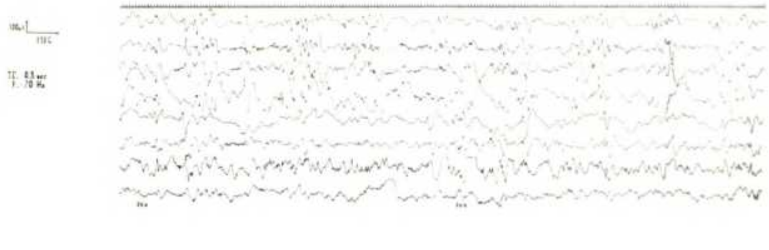

Fig. 5 *Case 2. EEG recorded at the age of 6 months. Upper: Awake EEG. Lower: Sleep EEG. Gross abnormalities mainly on the right*

The patient was treated with ACTH, phenobarbitone, and clonazepam. The spasms then stopped, the hemiparesis cleared almost completely, and the EEG improved. The ACTH was gradually removed from her treatment. Two months after the initial attack she was taking phenobarbitone and clonazepam, and the only remaining symptoms were mild spasms of short duration in the right arm twice a week.

Discussion

The proper evaluation of the ocular signs in female infants with spasms in flexion is the responsibility of the clinical ophthalmologist, who can exclude or establish the diagnosis of Aicardi's syndrome. Each patient may present a different ophthalmoscopic picture, but there are points in common suggesting the diagnosis of the syndrome.

The examination for the basic visual function of our patients showed normal responses to photic stimuli and normal fixation and following movements. In other reports the eyes have been found to show more pronounced anomalies and impaired visual function (Aicardi and Chevrie, 1969; Rousselie and Fontaine, 1971). The pupils in our patients were normal in size, shape, and reaction. Other reported cases have shown persistent pupillary membrane, anterior or posterior synechiae, and an abnormal or absent pupillary reaction to light (Aicardi *et al.*, 1969; Hoyt *et al.*, 1978). Strabismus has been reported in some cases (Rousselie and Fontaine, 1971), but in our patients we found no strabismus or abnormal ocular motility. Although microphthalmos or exophthalmos are reported by Aicardi *et al.* (1969), the appearance of the eyes in our patients was normal.

Hoyt *et al.* (1978), discussing the possibility of an infectious agent contributing to the pathogenesis of Aicardi's syndrome, refer to the observation of an inflammatory reaction in the anterior vitreous in one of their patients. The clear vitreous in both eyes of our patients does not support this view.

The most interesting ophthalmological findings in Aicardi's syndrome are those of the fundus. The optic disc in our patients was normal in both eyes. Excessive pigmentation in the peripapillary area was observed in the eye with the more severe chorioretinal lesions. Colobomas of the optic disc, reported fairly often, were not seen in our cases. Aicardi *et al.* (1969) have found 4 colobomas of the optic disc in 15 patients and Hoyt *et al.* (1978) 3 in 4 patients. Moreover, preretinal masses of glial tissue noted in other reports (for example, Rousselie and Fontaine, 1971) were not observed in our cases. The retinal vessels in the 4 eyes we have examined were normal. The haemorrhages in the retina reported by Deodati *et al.* (1974) were obviously a transient phenomenon.

The pathognomonic ocular feature of Aicardi's syndrome is the chorioretinal 'lacuna.' Aicardie (1965) in his original report describes the lacunae as areas of white-yellow colour ranging in size from 0·1 disc diameter to twice that of the normal disc. In our own cases lesions were found in both eyes. Comparing these lesions with those seen in fundus photographs of similar reports, we conclude that there are 2 main types of chorioretinal lesions. The first is the large and well defined hypopigmented lacuna with irregular pigment clumping at its border. Two such large lesions were found in the right eye of our case 1. The second is the small yellow lesion found in both eyes of our patients. It is important at this point to emphasise that the small lesions are as pathognomonic as the large ones for the diagnosis of Aicardi's syndrome when the other 2 criteria are present, namely, the spasms in flexion and the agenesis of the corpus callosum. An additional diagnostic feature is the small amount of pigment which surrounds large and small lesions and is in contrast with their distinctly hypopigmented central area (Aicardi *et al.*, 1965). This can be taken as a point of differentiation from other types of chorioretinal lesions.

We conclude from our 2 cases that the main assistance the clinical ophthalmologist can offer in the diagnosis of Aicardi's syndrome is the proper evaluation of the chorioretinal lesions.

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British Journal of Ophthalmology, 1979, 63, 718

Notes

Elderly persons

A multidisciplinary seminar on the 'Elderly person with failing vision—the problems and how best they can be met' will be held on 6 November 1979 at New Addenbrooke's Hospital, Hills Road, Cambridge, by the Department of Geriatric Medicine, Cambridge, jointly with the Disabled Living Foundation. Details from Miss Margaret Dowden, Conference Secretary, Disabled Living Foundation, 346 Kensington High Street, London W14 8NS (tel. 01-602 2491).

Contact lens technology

The annual course in contact lens technology will be held at the Cullen Eye Institute, Baylor College of Medicine, Houston, Texas, on 29 November–1 December 1979. Further details from David Paton MD, Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin (NC 200), Houston, Texas 77030, USA.

Glaucoma

The 29th annual symposium on glaucoma will be held at the New Orleans Academy of Ophthalmology on 22–26 March 1980. Details from Paula Di Leo, Executive Secretary, New Orleans Academy of Ophthalmology, 931 Canal Street, Suite 517, New Orleans, LA 70112, USA.

Afro-Asian Congress

The VIIth Afro-Asian Congress of Ophthalmology will take place in Tunis on 26–29 October 1980. The provisional programme has for its main subjects 'Virus eye diseases' and 'Trauma of the eye'; for its symposia 'Ocular microsurgery', 'Fundus in metabolic diseases'; 'Onchocercosis', 'History of ophthalmology', and 'Educational trends in ophthalmology'; and for round table discussions 'Paramedicals and prevention of blindness', and 'Traditional medicine'. Further details from the Secretariat, Institut d'Ophthalmologie, Bab Saadoun, Tunis, Tunisia.

Road safety

The 2nd International Congress on Vision and Road Safety, sponsored by the International Road Safety Council, will be held at the International Conference Centre in Paris (Porte Maillot) on 20–22 November 1980. Subjects under discussion will be night vision, road lighting, vehicle lighting, traffic signals, and reflecting signals. Registration fee is Fr750. Further information from R. Pansard, General Secretary, Linas 91310, Montlhery, France.

Correction

In the paper entitled 'Ocular and cardiovascular effects of local and systemic pindolol' (*BJO*, 1979, 63, 63–66) by Smith, S. E., Smith, S. A., Reynolds, R., and Whitmarsh, V. B., the caption to Table 1 contained an error. The concentration of plasma pindolol should have been given in nmol/l instead of μmol/l.

Change in style of references

In accordance with the Vancouver agreement many medical journals are to standardise the instructions they issue to authors on the preparation of articles. References will be cited by the numerical system already familiar in many journals, including the *British Medical Journal.*

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1 Green A B, Brown C D, Grey E F. A new method of measuring the blood glucose. *Br J Ophthalmol* 1980; 64:27–32.

2 Green A B, Brown C D. *Textbook of Medicine.* London: Silver Books, 1980.

3 Grey E F. Diseases of the pancreas. In: Green A B, Brown C D, eds. *Textbook of Medicine.* London: Silver Books, 1980; 349–362.

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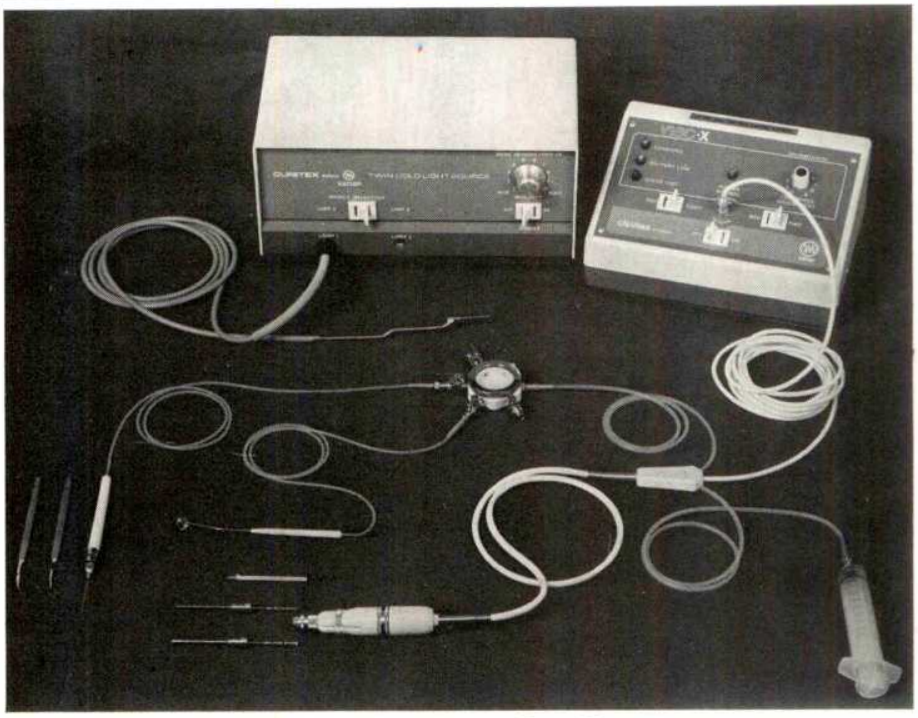

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This Symposium, like the three previous Mackenzie Symposia which were published in book form, is edited by Mr J. Stanley Cant of the Tennent Institute of Ophthalmology, Glasgow. This Part also contains the Proceedings of the Scottish, Irish, and regional ophthalmological societies, the full text of the Symposium on Retinal Therapy held at St. Thomas's Hospital, London, in November 1977, and the Annual Index for the year 1977.

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Drs. David G. Campbell, U.S.A.; Raymond Etienne, France; H. Fanta, Austria; S. Fyodorov, U.S.S.R.; W. Richard Green, U.S.A.; K. Iwata, Japan; Paul L. Kaufman, U.S.A.; C. E. T. Krakau, Sweden; Mikhail M. Krasnov, U.S.S.R.; Marvin L. Kwitko, Canada; Maurice E. Langham, U.S.A.; Adolphe A. Neetens, Belgium; A. P. Nesterov, U.S.S.R.; Harry A. Quigley, U.S.A.; Alan L. Robin, U.S.A.; Katsuzo Segawa, Japan; E. van Beuningen, Germany; Pal Weinstein, Hungary; Jacob T. Wilensky, U.S.A.; Thom J. Zimmerman, U.S.A.

Monday, March 10: Session II,
Drs. Robert K. Abraham, U.S.A.; E. Balestrazzi, Italy; O. P. Benedikt, Austria; Michael Blumenthal, Israel; Bruno Boles-Carenini, Italy; M. G. Bucci, Italy; Edward Grom, Venezuela; Enrique Gutierrez, Venezuela; Ryozo Kimura, Japan; Norman S. Levy, U.S.A.; Edoardo Maselli, Italy; Irvin P. Pollack, U.S.A.; Svatopluk Rehak, Czechoslovakia; Ralph S. Sando, U.S.A.; G. Scuderi, Italy; Gerald Stiegler, Switzerland; Uriel Ticho, Israel; Zarko M. Vucicevic, U.S.A.; R. Witmer, Switzerland.

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Tuesday, March 11: CATARACT/INTRAOCULAR LENS SURGERY SEMINAR.
Chairman: Richard C. Troutman, MD, State University of New York, Brooklyn. Speakers: John J. Alpar, MD; Robert F. Azar, MD; Ronald W. Barnet, MD; Charles H. Bechert, II, MD; Michael Blumenthal, MD; H. Busse, MD; Helmut Fanta, MD; Jack Hartstein, MD; K. Buol Heslin, MD; Charles D. Kelmar, MD; P. Kroll, MD; Marvin L. Kwitko, MD; Donald L. Praeger, MD; Harold G. Schele, MD; Edward L. Shaw, MD; Steven, P. Shearing, MD; Robert M. Sinskey, MD.

Wednesday, March 12: STRABISMUS/PEDIATRIC OPHTHALMOLOGY SEMINAR.
Chairman: Donelson Manley, MD; Wills Eye Hospital, Philadelphia, Pa. STRABISMUS: Speakers: John S. Hermann, MD; David A. Hiles, MD; Phillip Knapp, MD; Suzanne Veronneau-Troutman, MD; PEDIATRIC OPHTHALMOLOGY: Speakers: Daniel Finkelstein, MD; Marvin Kwitko, MD.

Thursday, March 13: CORNEA AND EXTERNAL DISEASES SEMINAR.
Chairman: Claes H. Dohlman, MD, Professor and Chairman, Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary. Speakers: Mathea Allansmith, MD; H. Dwight Cavanagh, MD; Deborah Pavan-Langston, MD; Michael Lemp, MD; David Miller, MD; George O. Waring, III, MD.

Friday, March 14: CONTACT LENS SEMINAR
Chairman: Jack Hartstein, MD, Washington University, St. Louis, Mo. Speakers: Mathea R. Allansmith, MD; Perry S. Binder, MD; H. Dwight Cavanagh, MD; Dean Clements; Robert J. Crossen, MD; Oliver Dabezies, MD; Gerald Feldman, PhD; James M. Gordon, MD; Ellis Gruber, MD; Paul R. Honan, MD; Leroy Meshel, MD; Ken Michaile, MD; John Morgan, MD; Robert Morrison, MD; Bernard Slatt, MD; Harold A. Stein, MD.

Saturday, March 15: OCULOPLASTIC SURGERY SEMINAR.
Chairman: Pierre Guibor, MD, New York Medical College, New York, NY, and other eminent speakers.

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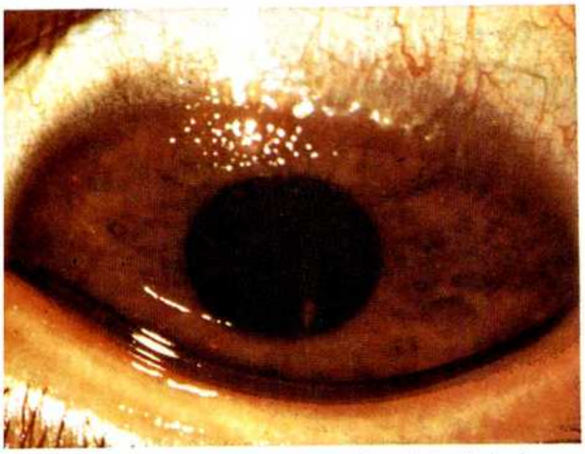

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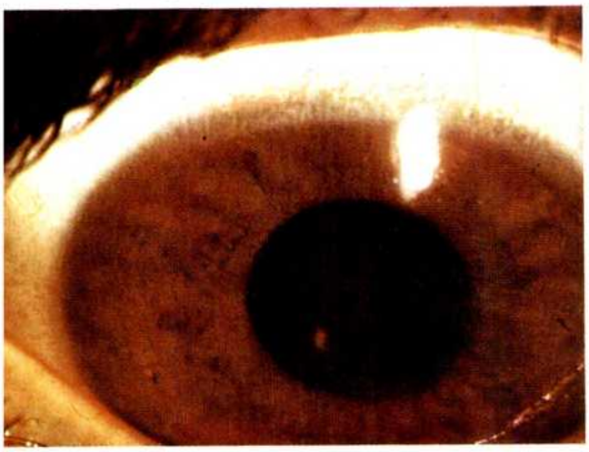

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*"Atopic conjunctivitis, conjunctivitis vernalis and the cromoglycate effect," in R. Voorhorst et al (Eds) "The Atopy Syndrome and Organ Challenge Procedures" (1973), Fisons BV, Zeist, p 71–3.

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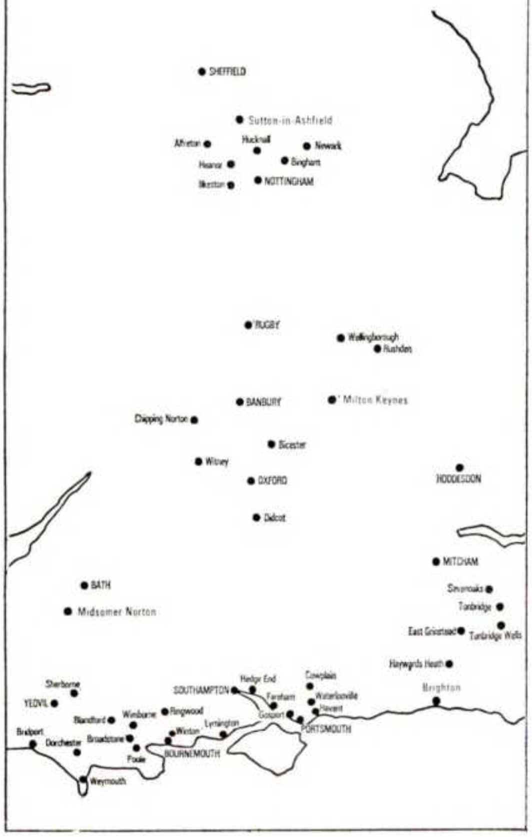

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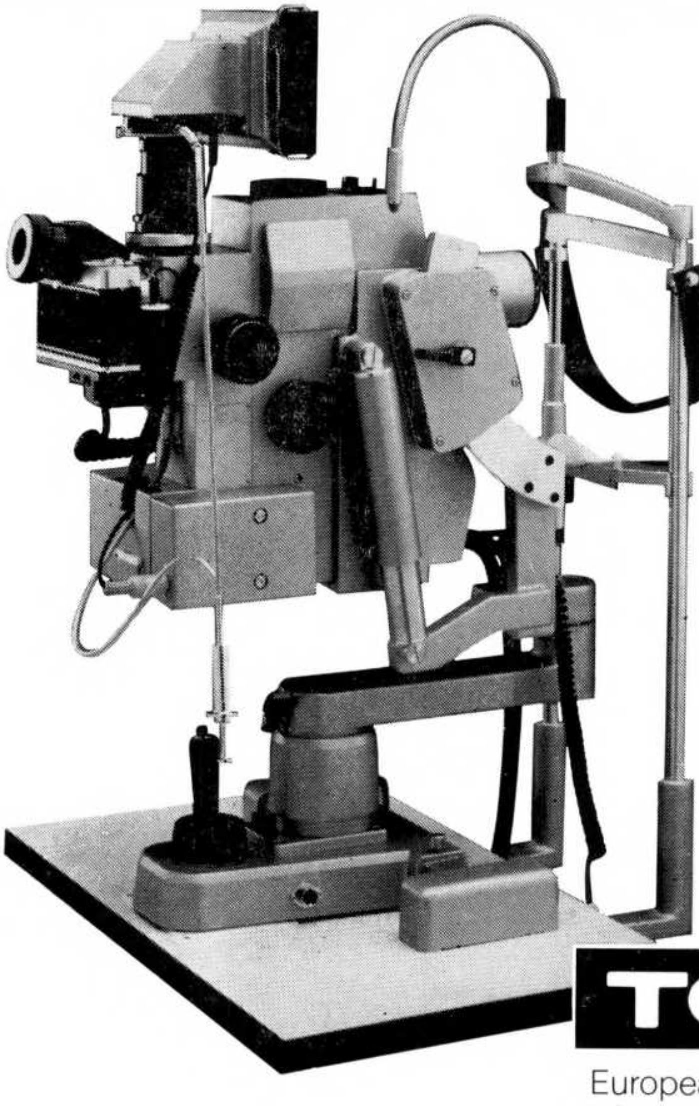

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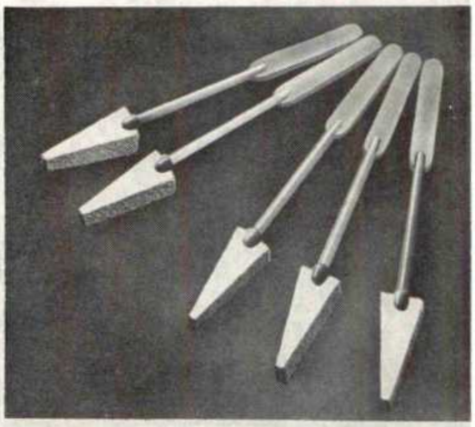

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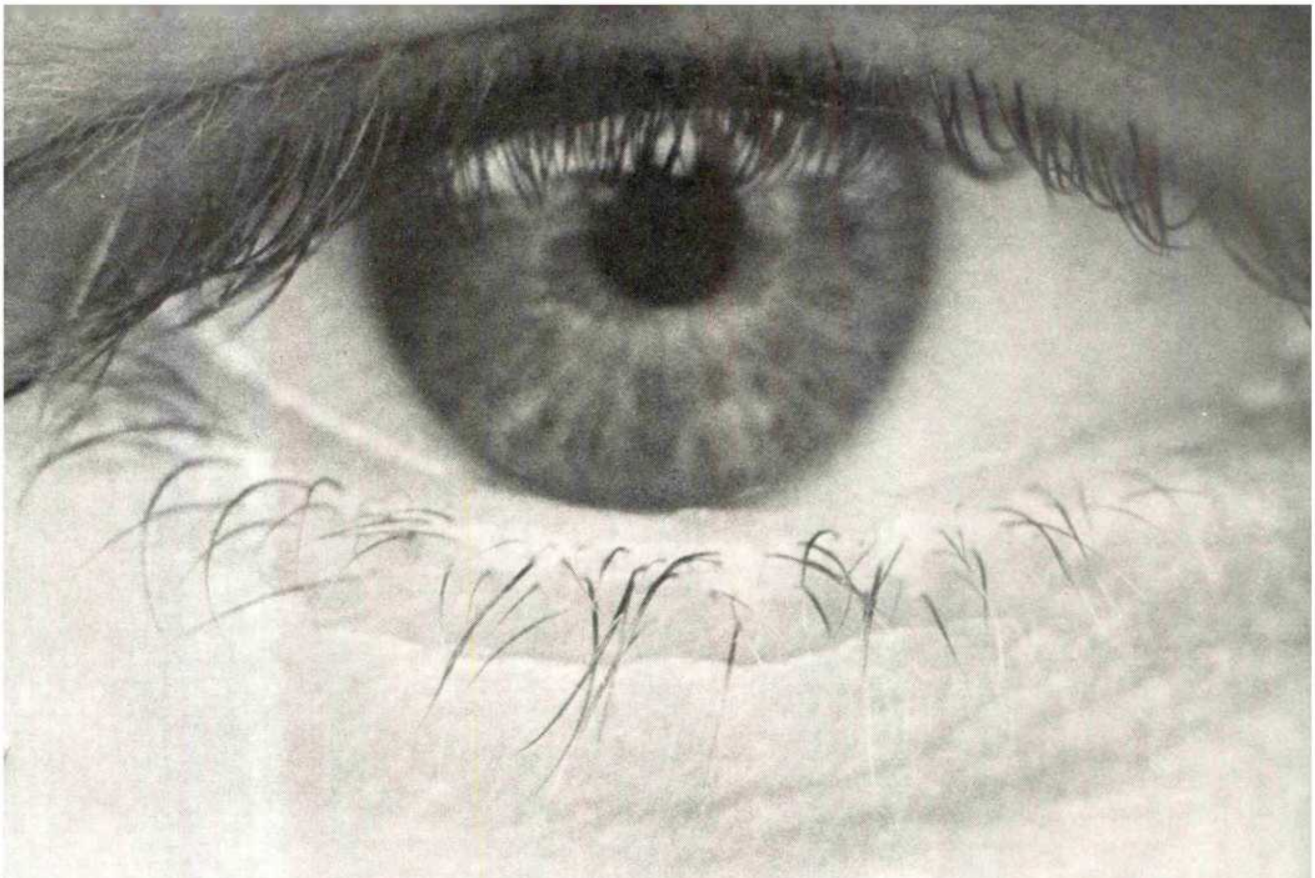

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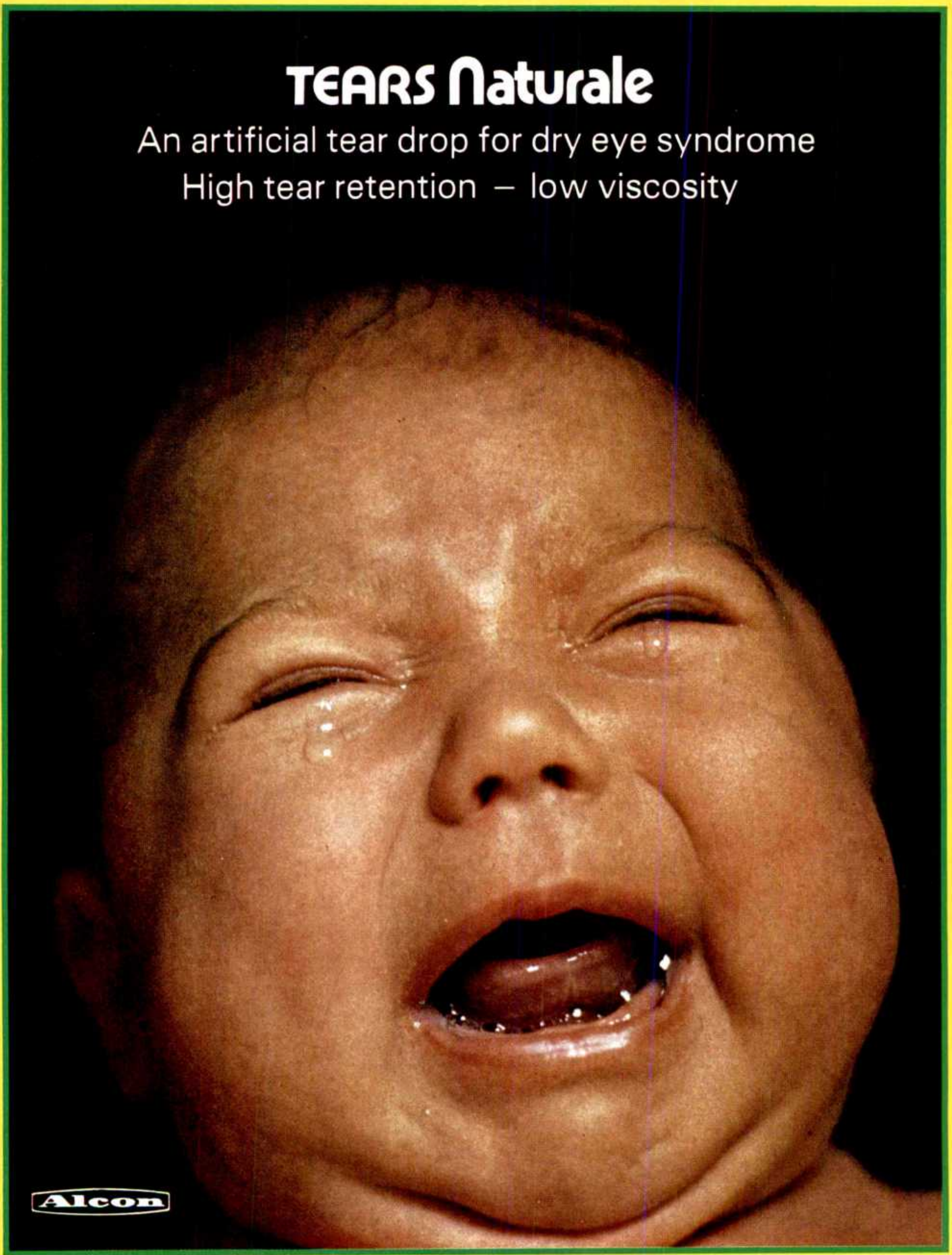
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British Journal of Ophthalmology, 1979, 63, 719

Editorial: International agency for the prevention of blindness

It is estimated that there are 28 million blind people in the world with category 3 visual impairment (less than 3/60) and 42 million with category 2 impairment (less than 6/60). This burden of blindness, the bulk of which is avoidable, is unlikely to be acceptable to world opinion if the facts are appreciated. General obstacles to the prevention of blindness have recently been outlined at a symposium held in Oxford (Jones, 1978).

Effective programmes to attack this problem require systematic community-based action in 4 stages. The first is to identify communities with a high prevalence of avoidable blindness. The second is to undertake an intensive phase of action among the most affected communities involving such measures as the correction of malnutrition, control of infection, and field surgery for the extraction of cataracts and the repair of lid deformities. The third consists in the delivery of simple therapeutic and preventive measures for the promotion of eye health, forming an integral part of primary health care. Lastly, central ophthalmic services should be assessed and if necessary strengthened to provide an adequate referral system and establish facilities for the training of paramedical personnel.

The multidisciplinary nature of these activities means that they cannot be undertaken by ophthalmologists alone. What is required is a managerial structure to deliver ophthalmic and other services to underserved communities.

The International Agency for the Prevention of Blindness arose because of the obvious need for an international nongovernmental organisation which could heighten the world conscience and tap resources through national organisations and also internationally through co-operation with the World Health Organisation. It comprises in the first place ophthalmologists, but members of organisations concerned with the welfare of the blind, medical and basic scientists, administrators, and other interested individuals are essential members. The agency can be successful only if ophthalmologists mobilise wide support for its aims and are seen to offer their skills and enthusiasm in concert with the contributions of well-wishers from other walks of life. So far the agency has worked closely with the World Health Organisation on such subjects as the strategy and operational aspects for the prevention of blindness and the collection of data concerning its incidence.

The IAPB wishes to hold its next general assembly at Asilomar immediately before the meeting of the international congress to be held in California in 1982. The objectives of this general assembly will include the following:

Planning. To convey to the membership, and particularly to the national committees, the policies and strategies for the prevention of blindness which have been developed by WHO, national governments, and IAPB, and to emphasise the need for multidisciplinary co-operation, national planning, and an integrated relationship to basic health programmes.

Conceptual. To encourage the development of concepts, philosophies, and techniques from a wide range of interested parties.

Educative. To attract the media to the practical possibilities of blindness prevention. This has been referred to as the 'climate changing' role of the agency—a role the IAPB can probably develop more successfully than any single academic or professional organisation.

Housekeeping. To elect the executive board, the regional chairmen, and the leadership; to approve affiliation with national committees, review the work of the administration, and ensure continuity.

Reference

Jones, B. R. (1978). General Obstacles to the Prevention of Blindness. *Transactions of the Ophthalmological Societies of the United Kingdom*, **98**, 316.

British Journal of Ophthalmology, 1979, 63, 720–724

Corneal ulceration following measles in Nigerian children

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From the [1]Department of Ophthalmology, Ahmadu Bello University Hospital, Kaduna, and the [2]Department of Medicine, Ahmadu Bello University, Zaria, Nigeria

SUMMARY Acute corneal ulceration in malnourished children is the commonest cause of childhood blindness in Northern Nigeria and usually develops after measles. Other severe diseases in malnourished children rarely precipitate corneal ulceration. A survey in a school for blind children showed that 69% of the children were blind from corneal disease, and a survey of children with corneal scars showed that at least 42% were caused by ulceration after measles. The clinical appearance of the active ulcers was very varied. The serum retinol-binding protein and prealbumin levels in children with corneal ulcers following measles were below normal, but a group of malnourished children without eye complaints following measles were found to have even lower levels. Thus a specific deficiency of vitamin A does not appear to be the primary cause of these ulcers, though it may be a contributory one. A specific measles keratitis and secondary herpes simplex infections may be local factors contributing to this ulceration, and there is nearly always a background of protein calorie malnutrition. Racial factors may also be of some significance.

Severe corneal ulceration following measles is a common condition throughout sub-Saharan Africa. In all reported surveys of child blindness it is a very significant cause and often it is overwhelmingly the most important cause. Phillips (1961) in Zambia estimated that 81% of blindness was caused by measles, and Awdrey *et al.* (1967), also from Zambia, surveying an area where corneal blindness was common, found that 80% of the total blindness was due to corneal lesions and half of these were caused by measles. In Malawi Chirambo and Ben Ezra (1976) considered that measles was the cause of 44% of child blindness. Sauter (1976), in Kenya, found that 47% of child blindness was due to xerophthalmia and two-thirds of these cases were precipitated by measles. Quéré (1964), from Senegal, found corneal scarring after measles to be the commonest cause of childhood blindness. In a hospital survey from Southern Nigeria Olurin (1970) found that only 14% of child blindness was caused by measles, and yet examination of the children in a blind school in Southern Nigeria showed that 33% of the inmates and 79% of the new admissions were blind from measles (Animashaun, 1977).

It is usually considered that this acute corneal ulceration is essentially a manifestation of vitamin A deficiency, so that a child with borderline vitamin A deficiency after contracting measles develops acute keratomalacia (Voorhoeve, 1966; Cobb and Awdrey, 1968; Oomen, 1971; Franken, 1974; Sauter, 1976).

In this paper we first assess the significance of measles as a cause of corneal ulceration and blindness in the local community and then compare the vitamin A status of children with corneal ulceration following measles to that of other children both well nourished and malnourished who contracted measles but did not develop any eye ulcers. Other factors that may contribute to the formation of these ulcers are then considered.

Patients and methods

All the children in Gindiri Blind School, the only school for visually handicapped children in Northern Nigeria, were examined to determine the cause of blindness. In some cases it was possible to obtain either from the children or the school records a history of any disease which precipitated the blindness. Seventy-four children were seen in 1975 and a further 30 in 1978. Because the pattern of pathology was not significantly different on the 2 occasions, the results of the 104 children seen in all are presented together.

All patients presenting at the Ahmadu Bello

Correspondence to Mr J. H. Sandford-Smith, FRCS, Department of Ophthalmology, Leicester Royal Infirmary, Welford Road, Leicester.

University Hospital, Kaduna, over a 3-month period February to April 1978 with a corneal scar from early childhood were examined and questioned to determine the cause of the original disease. Because most children attended with their mothers we could get a much more accurate description of the original illness. Also, this group included patients with disease in 1 eye only, who would not be seen in a blind school. Eighty-nine patients in all were seen in this group.

Seventy children were also seen at the Ahmadu Bello University Hospital, Kaduna, with acute, active corneal ulcers over a 12-month period in 1977–8. Particular note was made of any systemic disease which precipatated the ulceration and also the clinical appearance and morphology of the ulcers. The last 22 of these 70 children were investigated further to determine in particular their general nutritional and vitamin A status as follows: (*a*) Their weight for age was assessed according to the Harvard standard (Jelliffe, 1966), and tabulated as recommended by the World Health Organisation (1971). (*b*) Serum retinol-binding protein and prealbumin levels were estimated by the gel immunodiffusion method of Mancini using monospecific antisera (Behringwerke) and a standard human serum (Behringwerke) which contained known amounts of retinol-binding protein and prealbumin.

Their mean age was 22 months, range 9–72 months, and they presented on average at 13 days (range 5–30 days) after measles. For comparison retinol-binding protein and prealbumin levels were also estimated on the following age-matched children within 1 month of their having measles and without any evidence of eye ulceration: 12 well nourished children (more than 80% weight for age of Harvard standard), and 12 malnourished children. Seven of the children in this group were marasmic, and 3 had marasmic kwashiorkor and 2 kwashiorkor.

Table 1 *Causes of blindness of 104 children in Gindiri Blind School, Northern Nigeria*

Cause of blindness	*Total no.*	*% of total*
Phthisis bulbi, staphyloma, or corneal scarring	72	69·2
Retinal degeneration	12	11·5
Optic atrophy	5	4·9
Uveitis	5	4·9
Glaucoma	4	3·8
Cataract	3	2·9
Undertermined	2	1·9
Normal	1	0·9
Total	104	100

Table 2 *Probable original cause of corneal scar in 89 outpatients presenting with corneal scarring*

Probable cause	*Bilateral scarring*		*Unilateral scarring*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Measles	21	54	16	32	37	42
Trauma	1	3	10	20	11	12
Smallpox	3	8	2	4	5	6
Trachoma	4	10	1	2	5	6
Herpes simplex	—	—	6	12	6	7
Ophthalmia neonatorum	—	—	2	4	2	2
Vernal eye disease	1	3	—	—	1	1
Phlyctenular conjunctivitis	—	—	1	2	1	1
Congenital	—	—	1	2	1	1
Unknown	9	23	11	22	20	22

Table 3 *Precipitating disease in the 70 children with active corneal ulceration*

Disease	*No. of patients*	*% of total*
Measles	63	90
Gastroenteritis	3	4
Acute malnutrition	2	3
No antecedent disease	2	3

Results

The results of the blind school survey are shown in Table 1. When the children were questioned to assess the cause of the original corneal disease, about half attributed their blindness to measles. One case was due to an injury, two to smallpox, and the remainder were unable to give any description of their original illness.

The results of the hospital survey of patients with corneal scarring is shown in Table 2. The significance of measles is further shown in comparing the ocular damage produced by it to the damage produced from other causes. Of the eyes affected by measles 19 had useful vision, 21 no useful vision, and 18 total destruction of the eye. Of the eyes affected by other inflammations (i.e., all those except the trauma and unknown groups) 22 had useful vision, 6 no useful vision, and 1 had total destruction of the eye.

The precipitating disease in the 70 children with active corneal ulceration is shown in Table 3.

CLINICAL APPEARANCE OF ULCERS

The morphology of the active ulcers was very varied, often differed in the 2 eyes, and changed as the disease progressed. In only a few patients was it possible to observe the disease throughout its course, and in most cases severe ulceration had developed when the patient was first seen. (The changes recorded are those when first seen.) The ulcers were classified according to their appearance as follows:

Superficial punctate keratitis. This was seen in the early acute stage of measles. It was always bilateral and often associated with diminished tear production. Although this might progress directly to frank ulceration, there was sometimes a delay of a few weeks before the onset of ulceration.

Superficial ulcers. These were very irregular in distribution and varied in appearance from being very localised or dendritic, through more widespread involvement or 'geographical', to very extensive involvement or 'amoeboid'.

Deep stromal ulcers. These were mostly central or below the centre, but a few were very irregular in distribution. Seventeen out of 42 of these ulcers showed evidence of perforation.

Total corneal necrosis. This was obviously the most severe type of ulceration in which the entire corneal stroma had disappeared leaving the iris covered with a mixture of mucus, fibrin, and pus.

Exposure keratitis. In some cases the ulcer was localised to the lower cornea and had a clearly defined horizontal upper border, as is typical of exposure keratitis.

The incidence of the different types of ulcer and whether they were unilateral or bilateral is shown in Table 4. Several children had ulcers on other parts of the body. Sixteen had mouth ulcers, 1 of whom also had an ulcer of the thumb that she sucked; 1 had cancrum oris, 1 had an eyelid ulcer, and 1 had vulval ulcers.

Immunofluorescent staining or viral culture on eye scrapings from 34 of these children with active corneal ulcers after measles detected herpes virus in 16 and measles virus in 4 (see Whittle *et al.* (1978) for full details. This was part of a different study on some of the same group of patients).

Table 4 *Clinical appearance in 70 children with active corneal ulceration*

Type of ulcer	*Unilateral cases (other eye normal)*		*Bilateral cases*	
	No.	*%*	*No.*	*%*
Superficial punctate keratitis	0	0	8	20
Epithelial ulceration	9	31	9	22
Stromal ulceration	16	55	13	32
Total corneal necrosis	3	10	5	12
Exposure keratitis	1	3	6	15
Total	29		41	

Table 5 *Nutritional status of the last 22 children with active corneal ulceration*

Weight	*No oedema*	*Oedema present*
More than 80% Harvard standard weight for age	Normal 8	--
Between 60–80% Harvard standard for age	Underweight 8	Kwashiorkor 1
Less than 60% Harvard standard weight for age	Marasmic 4	Marasmic kwashiorkor 1

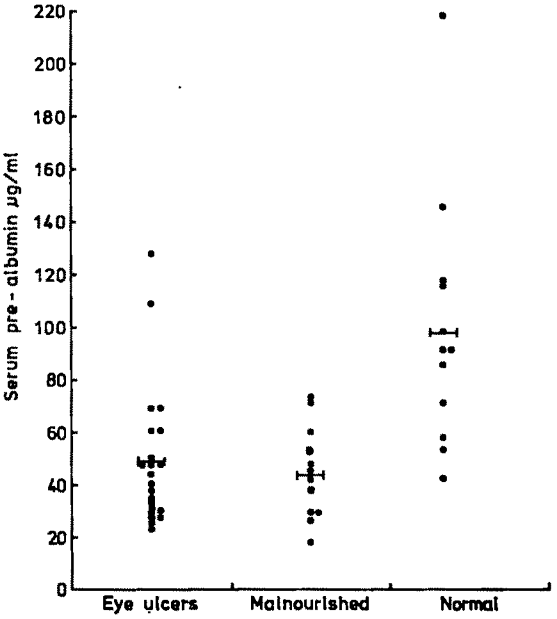

Fig. 1 *Serum prealbumin levels in children with acute ulcers, malnourished children, and well nourished children. The mean for each group is also shown*

NUTRITIONAL STUDIES

The weight for age of the 22 children in whom this was measured is shown in Table 5.

The serum prealbumin levels in these children and in the 12 well nourished and 12 malnourished children after measles but with normal eyes are shown in Fig. 1. There was no significant difference between serum prealbumin levels in those with eye ulcers and the malnourished children without eye ulcers. They averaged 48·3±SD 27·5 µg/ml and 45·1±SD 14·5 µg/ml respectively.

The serum retinol-binding protein levels for

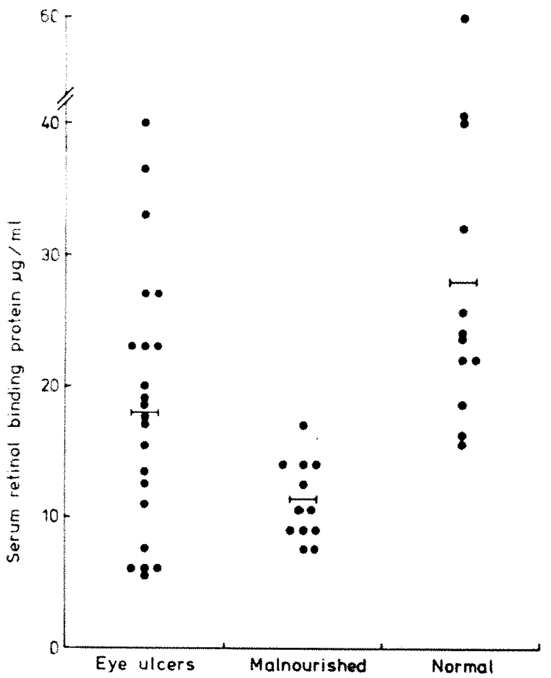

Fig. 2 *Serum retinol-binding protein levels in children with acute ulcers, malnourished children, and well nourished children*

these same children is shown in Fig. 2. There was a significant difference ($P<0{\cdot}05$) between serum retinol-binding protein levels in those with eye ulcers and the malnourished children without eye ulcers. They averaged 18·5±SD 10·0 µg/ml and 11·3±SD 2·9 µg/ml respectively. Fourteen out of the 22 children with eye ulcers had retinol-binding protein levels in the normal range. These tended to be the better nourished children, a fact supported by the positive and significant correlation between retinol-binding protein and prealbumin levels in these children ($r=+0{\cdot}48$, $P<0{\cdot}05$).

Discussion

The studies we have carried out on blind school children and on outpatients with corneal scars from early childhood confirm the results of other workers in different parts of sub-Saharan Africa that corneal ulceration is the commonest cause of child blindness and measles the commonest cause of corneal ulceration. However, the studies on children with active ulcers do not support the theory that this condition is primarily a manifestation of vitamin A deficiency, though it may often be a factor of some significance.

More than half the children with active ulcers had retinol-binding protein levels within the range of normal, and the mean retinol-binding protein level was higher in the children with active ulcers than in a group of malnourished children without ulcers.

The lesions are often unilateral, 29 out of 70 cases in this series (41%). In several instances one eye was grossly affected and the other eye completely normal, with no conjunctival xerosis or tear film abnormalities. This would obviously be impossible in true vitamin A deficiency.

Vitamin A deficiency is often precipitated by acute infection, but in this study severe and debilitating childhood disease other than measles only very rarely predisposes to corneal ulceration. Gastroenteritis in particular, which attacks children in the vulnerable postweaning period, is often associated with extreme malnutrition, and has a very high mortality rate, was the precipitating cause of ulceration in only 3 (4%) of these cases.

In addition the early stages of xerophthalmia are very rarely seen in this area even in malnourished children attending nutrition clinics, and the ulcers once present do not seem to respond to vitamin A treatment. The disease appears to be common in Southern Nigeria, where red palm oil (one of the best known sources of vitamin A) is a basic food stuff. In a recent survery of children with measles from Lagos, in Southern Nigeria, almost 1% were blinded by corneal ulceration (Animashaun, 1977). Although red palm oil is not widely used in this part of Nigeria, carrots, tomatoes, and mangoes are all available at different times of the year, and recall dietary investigation of children with measles and malnutrition would indicate that dietary vitamin A is not grossly deficient.

The relationship between vitamin A deficiency and protein calorie malnutrition is complex. Vitamin A is stored in the liver and distributed to the tissues bound to retinol-binding protein. This will fall in protein malnutrition, thus causing a tissue deficiency of vitamin A even in the presence of potentially adequate vitamin A in the diet. This has been demonstrated by giving malnourished children diets containing no significant vitamin A, and the serum retinol and retinol-binding protein both returned to normal (Igenbleek *et al.*, 1975). Moreover, acute measles can produce a protein-losing enteropathy, thus lowering even further the levels of retinol-binding and serum protein (Dossetor and Whittle, 1975).

Protein calorie malnutrition is obviously a significant background factor in the pathogenesis of these ulcers. Many of the children with acute ulcers were malnourished as shown by their weight for age and serum prealbumin levels, and there was a tendency for more severe ulceration to be seen in

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the more malnourished children. Thus all the 5 children with bilateral total corneal necrosis were clinically malnourished and 3 of them were marasmic. By contrast there were 10 children with active ulcers who were considered to be well cared for and well fed, and who all had a weight for age over 80%, and 8 of these 10 had only unilateral ulceration.

Measles itself appears to be a significant factor, as shown by the marked superficial punctate keratoconjunctivitis and diminished tear production in the early stages of the disease. This was first observed by Trantas (1907) and has recently been noted in detail in malnourished children in Kenya (Dekkers, 1978).

Measles and malnutrition are known to produce depression of the cellular immunity, thus predisposing to secondary herpes infections. The morphology of many of the ulcers was typical of herpes in an immunosuppressed patient, and this has been confirmed by culture and immunofluorescence studies (Whittle *et al.*, 1978). It is possible also that measles has a local effect in specifically triggering herpes infections of the eye and mouth. By contrast, in a survey of 500 cases of meningococcal meningitis under the age of 5, 15% developed herpetic vesicles of the face but none were in the eye, and they all recovered quickly (Whittle, unpublished).

Many of these children lie dehydrated and exhausted in a hot atmosphere, and lid closure becomes defective, leading to desiccation and ulceration of the exposed lower cornea.

Paediatricians who have worked both in Asia and in Africa often comment on the increased severity of measles in Africa, which may be racial. In Asian communities where xerophthalmia is rife measles does not seem to have such significance in causing corneal ulceration. It is interesting that one of the few reports describing postmeasles ulceration from outside Africa is from Haiti, a Negro community (Girard *et al.*, 1969).

For local treatment of the individual case we would emphasise prevention of exposure changes to the cornea in the acute stage of the illness by local care to the eyes, the application of oily antibiotic drops or ointment, and if necessary careful padding. For ulceration developing later we would stress the use of antiviral agents as well as local and subconjunctival antibiotic agents, and debridement may also be helpful.

Nearly always the general condition of the child requires urgent treatment also, which is obviously beyond the scope of this paper. Adequate parenteral or oral vitamin A must always be given.

In conclusion, postmeasles corneal ulcers are obviously caused by a variety of interacting factors, but it is important to try to identify which are the most significant of these in order to plan an effective programme of prevention of blindness in childhood. It would seem to us that measles vaccination is likely to be more effective than efforts to improve the general nutritional or vitamin A status of the community.

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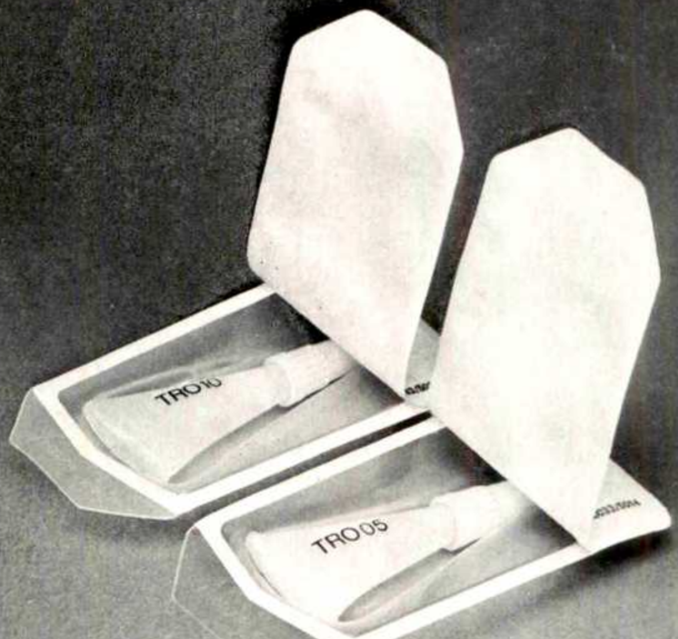

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Xenon arc panretinal photocoagulation for central retinal vein occlusion: a randomised prospective study*

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SUMMARY Thirty-three patients with central retinal vein occlusion were evaluated for the effects of scatter xenon arc panretinal photocoagulation. Thirty-four eyes (2 eyes of 1 patient) were randomly divided into a treatment (15 eyes) and a nontreatment group (19 eyes). The average follow-up per eye has been 29 months. The visual prognosis was not significantly better in either group. There was no difference in the development of fundus neovascularisation between groups. None of the patients in the treated group developed rubeosis or neovascular glaucoma. Two patients in the nontreatment group initially had rubeosis and 3 developed it after entry. All 5 involved eyes developed neovascular glaucoma. A significantly greater amount of central retinal capillary drop-out was present in the untreated eyes that developed rubeosis than those untreated eyes which did not. The eyes in the treated group had a similar range of capillary drop-out area, but none of these eyes developed rubeosis or neovascular glaucoma. Panretinal photocoagulation prevented the development of rubeosis and neovascular glaucoma in susceptible eyes.

There has been little change in the prognosis for visual acuity and survival of the eye after central retinal vein occlusion since the original clinical description of this condition by Liebreich (1855). Poor visual acuity usually results from leakage or ischaemia of the macular venules. This process may eventually result in macular fibrosis and scar formation or retinal atrophy (Raitta, 1965; Hayreh, 1971).

The therapy of central retinal vein occlusion is controversial. Numerous clinical regimens have been in vogue, each with varying degrees of reported success. None has been satisfactorily proved to be advantageous. Therapeutic trials have included the use of the following: potassium iodide and pilocarpine (Braendstrup, 1950), irradiation (Gradle, 1937; Hessberg, 1944; Guyton and Reese, 1948), anticoagulants (Holmin and Ploman, 1938; Klien and Olwin, 1956; Vannas and Orma, 1957), fibrinolytic agents (Dolenek *et al.*, 1968; Kohner *et al.*, 1976), dextran (François and Verbraeken, 1974), corticosteroids (Van Loon, 1961; Mehlan *et al.*, 1974), and carbogen (95% O_2 and 5% CO_2) (Sedney, 1976).

Definite therapeutic effects have been achieved with the use of photocoagulation in diabetic eye disease (Diabetic Retinopathy Study Group, 1976). Promising results have also been reported with the use of photocoagulation in branch vein occlusion and central retinal vein occlusion (Krill *et al.*, 1971; Campbell and Wise, 1973; Gitter *et al.*, 1975). The most significant effect noted thus far in retrospective nonrandomised studies of panretinal photocoagulation for central retinal vein occlusion has been the prevention or elimination of rubeosis iridis and subsequent neovascular glaucoma (Krill *et al.*, 1971; François *et al.*, 1974; Freyler and Nichorlis, 1974; Theodossiadis *et al.*, 1974; Wetzig and Thatcher, 1974; Zweng *et al.*, 1974; Oosterhuis and Sedney, 1975; Callahan and Hilton, 1974; Fetkenhour *et al.*, 1975; Little *et al.*, 1976; Sedney, 1976).

In 1976 we reported the preliminary results of the first prospective controlled study to evaluate the efficacy of xenon arc panretinal photocoagulation in the treatment of central retinal vein occlusion

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(May *et al.*, 1976). The first 20 patients in the study were evaluated after an average follow-up of 18 months. There was no difference in the visual prognosis between groups. In the untreated group 4 patients developed rubeosis that progressed to neovascular glaucoma (NVG), but none of the patients in the treated group developed rubeosis or NVG. Photocoagulation had no significant effect on the development of disc or retinal neovascularisation. Similar results were reported by Laatikainen *et al.* (1977) in a more recent study.

This is the second report of the prospective randomised study of xenon arc panretinal photocoagulation for central retinal vein occlusion from the University of Illinois Eye and Ear Infirmary. The study was begun in January 1973 and continued through March 1978. A total of 33 patients were included in the study. The average follow-up time after occlusion was 28·5 months with a range of 5 to 64 months.

Patients and methods

Patients older than 40 years of age who had clinical central retinal vein occlusion and vision less that 6/12 (20/40) in the involved eye were referred to us from clinic and private patient populations of the University of Illinois Eye and Ear Infirmary. Patients with systemic or ocular disease such as diabetes mellitus, which could greatly influence the ocular prognosis, were excluded from the study. Other patients excluded were those whose involved eye had media with insufficient clarity to permit photocoagulation; those who were or had been treated with anticoagulants, corticosteroids, or vasodilators after the time of the central vein occlusion; and patients with an occlusion prior to evaluation for a duration of more than 1 year. Two patients entered in the study did have clinically evident central retinal vein occlusions for a longer time (18 and 24 months), but they had been followed up in our ophthalmology clinic.

All examination and treatment procedures were explained to those patients eligible for the study. The protocol that was adhered to had been approved by the University of Illinois Medical Center Ethics Committee, and the study was monitored by 3 assigned ophthalmologists who were not participating in the study.

A thorough medical history was recorded and each patient was referred for systemic evaluation. The following laboratory tests were performed: a complete blood cell count, urine analysis, 3-hour glucose tolerance test, plasma thromboplastin, partial thromboplastin time, haemoglobin electrophoresis, serum protein electrophoresis, electrocardiogram, chest roentgenogram, red blood cell sedimentation rate, and serum cholesterol and triglyceride levels.

During the initial ophthalmological evaluation, the following examinations were performed: visual acuity (Snellen chart, refracted) slit lamp examination of the anterior segment, gonioscopy and fundus biomicroscopy, applanation tonometry, visual fields (Goldmann), fundus fluorescein angiography, and stereoscopic colour photography of the fundus. Fundus fluorescein angiography was repeated in 3 months and then annually. All other procedures were repeated 1 month after the initial evaluation and then every 3 months thereafter. Iris angiography was performed on all patients during the last 18 months of the study if there was a clinical suspicion of rubeosis.

Each patient was randomly assigned to a treatment or nontreatment group. The treated group underwent photocoagulation as outpatients as soon as possible after entry.

Dilatation consisted of 1 drop of 1% tropicamide and 1 drop of 1% cyclopentolate hydrochloride on the eye to be treated. This was repeated again in 10 minutes. Topical 0·5% tetracaine (amethocaine) and a retrobulbar injection of 2 ml of 2% lidocaine (lignocaine) with epinephrine (1:100 000) and hyaluronidase were given prior to treatment. Panretinal photocoagulation was performed through a widely dilated pupil with the xenon arc photocoagulator (model 514 Optical Radiation) using a Goldman three-mirror lens and a Fankhauser slit-lamp delivery system. A 360° scatter panretinal photocoagulation was administered in 1 or 2 sessions. The burns were kept at least 1 disc diameter from the disc and macula, and no scattered burns were placed within the temporal arcades. Central burns (within 5 disc diameters of the disc) were 3°, and those further peripherally were 4·5°. The number of burns and the energy delivery in joules were recorded at each treatment session. The burns were placed at least 3° apart. Focal photocoagulation was applied directly to neovascularisation on the retina (NVE). Neovascularisation from the disc (NVD) was not treated directly. A polymixin-B-bacitracin-neomycin ointment and an eye patch were applied to the eye after treatment. The patient was examined the next day, then every week for 1 month, and then at 3-month intervals.

The area of initial retinal capillary obliteration was quantitated for each eye entered in the study. The measurements were obtained retrospectively from fundus fluorescein angiograms and photographs (central 30° of the fundus with the macula at the centre) taken at the time of initial evaluation. A midvenous phase angiogram was projected on a screen with a colour slide of the same field shown beside it. This comparison was done to eliminate the confusion of those areas of retina obscured by haemorrhage with those having actual retinal capillary obliteration. The dimensions of the disc and the area of retinal capillary obliteration were measured on the projected fluorescein. Areas were calculated by standard geometric means in absolute terms (i.e., cm^2).

The absolute areas measured were relative to the projection magnification and as such have little significance when compared among patients. For this reason the area of retinal capillary obliteration was calculated in terms of disc areas for each eye. This was derived by dividing the area of capillary obliteration (cm^2) by the area of the disc (cm^2) of the same eye:

$$\frac{\text{area of retinal capillary obliteration } (\text{cm}^2)}{\text{area of disc } (\text{cm}^2)} = \text{area of retinal capillary obliteration (disc areas).}$$

This information is presented in Table 1.

Results

Thirty-four eyes of 33 patients were entered into the study (both eyes of 1 patient). Nineteen eyes were randomly assigned to the nontreated group and 15 to the treated group. The age range was 50 to 81 years (64 average) in the nontreated group and 41 to 88 years (63 average) in the treated group.

There was a very high incidence of glaucoma among our patients. Thirteen patients (39%) had glaucoma, 10 of whom had not been previously diagnosed for the condition. Seventeen (52%) were systemically hypertensive. Of these, 3 were previously undiagnosed and 1 was a known hypertensive who had declined to take medication. These and other basic entrance data are presented in Table 1.

The average follow-up time after the central retinal vein occlusion was 28·6 months per eye (a range of 8 to 56 months) in the nontreated group and 28·5 months (a range of 5 to 64 months) in the treated group. Two patients in the treated group had an insufficient follow-up time of less than 6 months. The time period between the onset of symptoms and entry into the study was an average of 4·0 months for the nontreated group and 3·0 months for the treated group. Distribution data for the patients are summarised in Table 2. The follow-up times for each patient are listed in Table 3.

All patients had clinical evidence of macular oedema on entry into the study. The average duration of the oedema, as shown by fluorescein angiography, was 17·5 months in the nontreated group and 21·2 in the treated group.

Only 1 patient did not have cystoid macular oedema (CME) at some time during the course of the study. The average duration of the CME in those eyes in which it resolved was 13·0 months for the nontreated group (12 eyes) and 11·1 months for the treated group (9 eyes). In 2 eyes of the nontreated group and in 3 eyes of the treated group the CME persisted for the duration of the study. The duration of CME could not be adequately followed up in 3 eyes of each group: 3 eyes of the untreated group developed cloudy media all secondary to NVG; 1 eye of the treated group had insufficient follow-up; 1 eye developed a total nonrepairable retinal detachment; and the macula of 1 eye was inadvertently photocoagulated.

Five patients in each group developed neovascularisation from the disc (NVD). The average onset after vein occlusion was 12 months for eyes in the nontreated and 4·2 months for the treated group. The NVD regressed after 8 months' duration in one nontreated eye and after an average of 3·7 months in 3 eyes of the treated group. The NVD persisted for the duration of the study in 4 eyes of the nontreated and 2 eyes of the treated group. Shunt vessels developed on the disc in 2 eyes of the nontreated group and in 4 eyes of the treated group. There did not appear to be a correlation among the development and persistence of macular oedema, CME, or NVD.

One patient in each group developed neovascularisation on the retina (NVE). Patient 31 in the nontreated group was lost to follow-up after the NVE was found. Patient 29 in the treated group had NVE present on entry to the study and was focally treated. The NVE did not resolve until it was focally retreated again 3 months later. The neovascularisation and macular oedema data for the patients are summarised in Table 4.

Two patients in the nontreated group had rubeosis initially. One of the 2 also had clinical evidence of NVE. Three additional patients in this group developed rubeosis after entry into the study. Four of the patients had clinical evidence of neovascular glaucoma (NVG) when the rubeosis was first noted, the other patient developed NVG within 4 weeks. The average time when NVG was first noted was 13·2 weeks or 93 days after the onset of central vein occlusions. None of the patients in the treated group developed rubeosis or NVG.

The nontreated patients who developed NVG had retinal capillary drop-out areas in the range of 16·0 to 22·0 (19·6 average) disc areas. Other eyes in the nontreated group had capillary drop-out areas in the range of 0 to 9 (2·1 average) disc areas. The

Table 1 *Entrance data*

Patient	*Age (yr)*	*Race*	*Sex*	*Involved eye*	*Primary open-angle glaucoma*	*Hypertension*	*Other medical problems**	*Group*	*Area of capillary obliteration (disc areas)*
1	72	B	M	OS	OU previously unknown	None		Nontreatment	18·8
2	66	B	M	OS	None	10 yr of therapy		Nontreatment	16·0
3	54	SA	M	OS	OU previously unknown	None		Treated	0
4	66	W	M	OS	None	5 yr of therapy		Treated	4·7
5	81	B	M	OS	OU previously unknown	Previously unknown	Positive FTA-ABS previously untreated	Treated	22·7
6	65	B	F	OD	OU previously unknown	5 yr of therapy	Sickle cell trait	Treated	0
7	59	W	M	OD	OU 9 mo of therapy	2 mo of therapy		Nontreatment	9·0
8	69	W	M	OS	None	None		Treated	5·1
9	61	B	M	OS	None	10 yr of therapy		Treated	4·2
10	73	B	F	OS	OU previously unknown	None		Nontreatment	21·4
11	48	B	F	OD	None	2 yr of therapy		Nontreatment	0
12	70	W	M	OS	None	Previously unknown		Nontreatment	0
13	67	W	M	OS	OU previously unknown	None		Treated	0
14	77	B	M	OS	None	None		Nontreatment	0
15	48	SA	F	OS	None	Previously unknown		Treated	15·2
16	88	B	F	OD	None	12 yr of therapy		Nontreatment	1·1
17	52	W	M	OS	None	None		Nontreatment	2·2
18†	64	SA	M	OS	None	None	Diabetes mellitus known for 7 mo	Treated	0
19	80	W	M	OD	OU previously unknown	None		Nontreatment	22·0
20	65	B	F	OD	None	8 yr of therapy		Nontreatment	0
21	73	W	M	OD	None	5 yr of therapy		Nontreatment	1·6
22	66	B	M	OS	None	10 yr of therapy		Nontreatment	0
23	53	W	M	OS	None	None		Treated	1·4
24	67	B	M	OS	OU 6 yr of therapy	None		Treated	12·8
25‡	61	SA	F	OU	OU previously unknown	None	Elevated serum cholesterol and triglycerides	OD nontreatment OS treated	4·6 0
26	76	B	F	OS	OU 5 yr of therapy	None		Nontreatment	0
27	41	B	M	OS	OU previously unknown	None		Nontreatment	19·8
28	76	B	F	OD	None	None		Treated	17·1
29	73	W	M	OS	OU previously unknown	2 mo of therapy		Treated	4·4
30	64	W	F	OS	None	5 yr of therapy		Nontreatment	2·8
31	77	B	F	OD	None	18 yr of therapy		Nontreatment	8·5
32	53	B	M	OS	None	Known for several years but previously untreated	MI & CHF Jan/77	Nontreatment	0
33	50	W	M	OD	None	None		Treated	0

*FTA-ABS indicates fluorescent treponemal antibody absorption test; MI, myocardial infarction; and CHF, congestive heart failure.

†The patient denied diabetes mellitus on entry into the study. After an abnormal glucose tolerance test, the patient admitted taking insulin for the past 7 months. There was no evidence of diabetic eye disease OD during the course of the study.

‡Both eyes were entered into the study.

Table 2 *Summary of data on patients*

	Nontreatment	*Treated*
No. of eyes*	19 11 OS 8 OD	15 12 OS 3 OD
Glaucoma†	7 patients	7 patients
Systemic hypertension	11 patients	6 patients
Average time elapsed before entry into study	4·0 mo	3·0 mo
Average follow-up postocclusion	28·6 mo	28·5 mo
Insufficient follow-up	0	2 patients

*Thirty-three patients were admitted to the study. Patient 25 had both eyes entered into the study.
†Thirteen patients admitted to the study had bilateral primary open-angle glaucoma, including patient 25 (OD was entered into the nontreatment group and OS into the treated group).

Table 3 *Patient follow-up time*

Patients	*Involved eye*	*Onset of symptoms*	*Time elapsed before entering study*	*Postocclusion follow-up time*
Nontreated				
1	OS	May/74	4 wk	8 mo
2	OS	Jan/74	4 wk	40 mo
7	OD	May/72	18 mo*	56 mo
10	OS	Jan/74	3 wk	40 mo
11	OD	May/73	24 mo*	54 mo
12	OS	Feb/76	3 mo	23 mo
14	OS	April/77	1 wk	8 mo
16	OD**	Feb/73	6 mo	17 mo
	OS	April/72	Not included in study	
17	OS	April/73	4 mo	51 mo
19	OD	March/73	3 mo	31 mo
20	OD	July/75	1 day	30 mo
21	OD	April/73	3 mo	56 mo
22	OS	Nov/75	5 days	22 mo
25	OD†	April/76	13 days	21 mo
26	OS	Feb/74	3 mo	21 mo
27	OS	April/76	2 days	14 mo
30	OS	Aug/76	2 mo	16 mo
31	OD	March/74	6 mo	20 mo
32	OS	Sept/76	1 wk	15 mo
	OD**	March/73	Not included in study	
Treated				
3	OS	May/73	6 wk	27 mo
4	OS	Nov/72	8 mo	64 mo
5	OS	Feb/76	1 mo	25 mo
6	OD	May/74	10 days	42 mo
8	OS	Oct/76	4 days	16 mo
	OD**	Sept/71	Not included in study	
9	OS	Oct/75	3 mo	28 mo
13	OS	April/75	3 wk	34 mo
15	OS	Nov/76	3 mo	12 mo
18	OS	Jan/77	2 wk	11 mo
23	OS	May/73	7 mo	8 mo‡
24	OS	June/73	4 mo	55 mo
25	OS††	May/76	10 days after entering study	20 mo
28	OD	June/77	7 wk	5 mo
29	OS	Jan/72	12 mo	59 mo
33	OD	June/74	2 wk	22 mo

*These patients had been followed up in the general eye clinic from within 3 months of their occlusions.
†OS entered in treated group.
‡Lost to follow-up one week after treatment.
††OD entered in nontreated group.
**The central retinal vein occlusions in these eyes had occurred too long previously to be included in the study; the other eye of each of these patients was included in the study.

average capillary drop-out for the entire nontreated group was 6·7 disc areas. The range was 0 to 22·7 (5·8 average) disc areas in the treated group (see Table 1).

Analysis of the distribution of the areas of retinal capillary drop-out at the initial evaluation showed a totally random distribution of eyes to both groups. By *t* test analysis there was a significance of $P=0·485$. This means that on the basis of the distribution of areas of capillary drop-out all eyes had an equal chance of being assigned to either group.

Five eyes in the untreated group developed NVG; none in the treated group developed it. This suggests that the panretinal photocoagulation prevented the development of glaucoma in the treated group. This is supported by Fisher's exact test at the 0·031 significance level.

Fifteen (52%) of the eyes entered into the study (excluding eyes developing NVG) had initial intraocular pressures lower than in the noninvolved eye. The initial pressures averaged 5 mmHg (range of 3 to 12 mmHg) lower and did not return to equal in the 2 eyes until an average of 6·1 months after occlusion. Three involved eyes of 3 patients had pressures of 3 mmHg or greater than in the non-involved eye. For the remainder of the patients the difference between the intraocular pressures of both eyes was within 2 mmHg.

Each of the 15 treated eyes in the group received an average of 208 burns with an average energy delivery of 173 joules. The range was from 120 to 335 burns per eye with a delivered energy range of 70 to 340 joules. Patients receiving the less dense photocoagulation patterns (140 burns or less) did not appear to differ in their ultimate prognosis. A high energy level was required for those eyes with greater amounts of nuclear sclerotic lens changes. A treatment summary for each patient is outlined in Table 5.

Three patients had peripheral choroidal effusions

Table 4 *Neovascularisation and macular oedema**

			Cystoid macular oedema		*NVD*		*NVE*		
Patient	***Onset***	***Duration***	***Onset***	***Duration***	***Onset***	***Duration***	***Onset***	***Duration***	***Other***
Nontreated									
1	I	DS (8 mo)	I	DS (8 mo)	None		None		Rubeosis on entry (4 wk) NVG at 8 wk
2	I	1 yr	I	12 mo	None		None		Rubeosis at 24 wk with NVG
7	I	18 mo	I	18 mo	1 mo	DS (56 mo)	None		Minimal NVD persisted; shunt vessels on disc
10	I	UE	I	UE	UE		UE		Rubeosis at 12 wk with NVG
11	I	2 yr	I	12 mo	12 mo	DS (54 mo)	None		Minimal NVD persisted
12	I	23 mo	I	12 mo	None		None		
14	I	DS (8 mo)	I	DS (8 mo)	None		None		
17	I	17 mo	I	17 mo	6 mo	14 mo	None		
19	I	UE	12 wk	UE	UE		UE		Rubeosis at 12 wk with NVG
20	I	6 mo	I	2 mo	None		None		
21	I	DS (56 mo)	I	12 mo	None		None		
22	I	DS (22 mo)	2 mo	12 mo	None		None		
25	I	14 mo	I	4 mo	None		None		
26	I	14 mo	I	6 mo	21 mo	DS (21 mo)	None		Lost to follow-up after NVD noted
27	I	UE	I	UE	UE		UE		Rubeosis and NVE at 10 wk
30	I	DS (16 mo)	I	6 wk	None		None		
31	I	DS (20 mo)	I	12 mo	20 mo		20 mo (did not return)		Total superior vein occlusion of other eye (OS)
32	I	5 mo	None		None		None		Inferior temporal branch vein occlusion in the same eye 20 mo before; shunt vessels on disc at time of CRVO
Treated									
3	I	DS (27 mo)	I	6 mo	12 mo	DS (27 mo)	None		NVD persisted a 1/2 disc diameter
4	I	36 mo	I	19 mo	None		None		Macular drusen OU; shunt vessels on disc
5	I	DS (24 mo)	I	10 mo	None		None		Tortuous shunt vessels on disc; total superior vein occlusion of other eye (OD)
6	I	DS (42 mo)	10 wk	DS (42 mo)	5 mo	DS (42 mo)	None		Minimal NVD persisted; tortuous shunt vessels on disc
8	I	DS (16 mo)	I	DS (16 mo)	None		None		
9	I	DS (28 mo)	I	10 mo	None		None		Familial drusen OU; tortuous shunt vessels on disc
13	I	NA	2 mo	NA	NA		NA		Total retinal detachment following photocoagulation
15	I	DS (12 mo)	I	5 mo	1 mo 7 mo		None		Minimal shunt vessels remained on disc
18	I	DS (11 mo)	I	4 mo	1 mo 4 mo		None		
23	I	Insufficient follow-up	I	Insufficient follow-up	Insufficient follow-up		Insufficient follow-up		Macular hole present
24	I	30 mo	I	27 mo	None		None		Tortuous shunt vessels on disc
25†	I	10 mo	I	4 mo	2 mo 4 mo		None		
28	I	DS (5 mo)	I	DS (5 mo)	None		None		
29	I	14 mo (macula dry 2 mo post-treatment)	I	15 mo	None		I (treated again 3 mo later and resolved)		
33	I	NA	I	NA	None		None		Macula accidentally photocoagulated

*I indicates present on entry into study; DS, present for duration of time followed up in study; UE, unable to evaluate due to ocular media haze; NA, not applicable; NVD, neovascularisation on the disc; NVE, neovascularisation on the retina; and NVG, neovascular glaucoma.
†Both eyes were entered into study.

Table 5 *Xenon arc photocoagulation group*

Patient	*Time treated postocclusion*	*No. of treatment sessions*	*Total burns*	*Energy delivered (joules)*	*Treatment problems and complications**
3	7 wk	1	139	105	Moderate NS
4	8 mo	1	335	160	Moderate NS
5	7 mo	1	140	220	Minimal 360° choroidal effusion; resolved within 2 wk
6	11 days	1	202	100	None
8	1 mo	2	308	340	Early NS; minimal 360° choroidal effusion resolved in 4 wk; macular haemorrhage 4 wk after treatment
9	8 mo	1	249	210	Early NS; iris burns
13	3 mo	3	231	295	Moderate NS; unrepairable retinal detachment 2 days after final treatment
15	4 mo	1	120	70	None
18	6 wk	2	240	176	A 60° schisis cavity was walled off with photocoagulation
23	7 mo	1	212	220	Intense retinal burns
24	4 mo	1	269	110	None
25	3 wk	1	138	140	Early NS; moderate 360° choroidal effusion resolved in 6 wk
28	7 wk	1	139	150	Moderate NS
29	4 wk	1	225	200	Moderate NS; iris burns
33	2 wk	1	173	95	Macula photocoagulated

*NS indicates nuclear sclerotic lens changes.

after photocoagulation, but these resolved without problems. Two eyes received iris burns during photocoagulation, and the macula of 1 eye was inadvertently photocoagulated. The eye of patient 8 developed a dense macular haemorrhage within 4 weeks after photocoagulation. The eye of patient 13 developed a nonrepairable tractional retinal detachment secondary to massive vitreous retraction within 2 days of the final treatment session. These eyes were treated heavily in 2 and 3 sessions, respectively. A summary of treatment data appears in Table 5.

Vision decreased in 8 eyes of the nontreated group, remained the same in 6 eyes, and improved in 5 eyes. The vision decreased in 7 of the eyes of the treated group, remained the same in 5, and improved in 3. There was insufficient follow-up of 2 patients in the treated group to evaluate visual change. The visual acuity changes for each patient are listed in Table 6.

Discussion

Focal and panretinal photocoagulation are beneficial in the treatment of some ocular vascular problems encountered with diabetes mellitus, sickle cell disease, and branch vein occlusion. It is now believed that the destruction of hypoxic retinal tissue by photocoagulation lessens the neovascular stimulus present in the eye (Krill *et al.*, 1971; Cleasby *et al.*, 1974). By decreasing the amount of tissue that is perfused, the remaining tissue may receive a more adequate supply of oxygenated blood. This ablation of retina also may decrease the retinal vascular load and decrease macular leakage and oedema (Campbell and Wise, 1973; Theodossiadis *et al.*, 1974). Also, the destruction of the pigment epithelium may promote the drainage of fluid into the choroidal circulation (Peyman *et al.*, 1971).

The 2 most significant factors predisposing our patients to ocular vein occlusion were primary open-angle glaucoma and systemic hypertension. Most of the patients (77%) with primary open-angle glaucoma were unaware of their problem, as were 18% of the systemically hypertensive patients.

Our patients' eyes were at a very high risk for multiple occlusive problems. Three of the patients had had a previous central retinal vein occlusion in their opposite eye which was not eligible for the study because of the duration of the occlusion. One of the patients had a branch vein occlusion pre-

Table 6 *Change in visual acuity*

Patient	*Eye*	*Initial vision**	*Final vision*	*Reason for final vision†*
Nontreated				
1	OS	LP	NLP	NVG
2	OS	6/21 (20/70)	NLP	NVG
7	OD	6/120 (20/400)	6/120 (20/400)	Pigment epithelial defect of macula
10	OS	1/100 (2/200)	NLP	NVG
11	OS	HM	HM	Macular scar
12	OS	6/60 (20/200)	1/40 (5/200)	Persistent macular oedema
14	OS	6/120 (20/400)	6/120 (20/400)	Persistent cystoid macular oedema
16	OD	1/100 (2/200)	1/100 (2/200)	Preretinal fibrosis
17	OS	6/120 (20/400)	1/40 (5/200)	Pigment epithelial defect of macula and preretinal fibrosis
19	OD	HM	LP	Mature cataract and NVG
20	OD	6/120 (20/400)	1/15 (20/50)	Disruption of macular pigment epithelium
21	OD	HM	HM	Macular scar
22	OS	1/40 (5/200)	1/40 (5/200)	Persistent macular oedema
25	OD	6/30 (20/100)	6/120 (20/400)	Macular scar
26	OS	1/66 (3/200)	6/120 (20/400)	Persistent macular oedema
27	OS	HM	NLP	NVG
30	OS	1/66 (3/200)	6/120 (20/400)	Persistent macular oedema
31	OD	LP	60/90 (20/300)	Persistent macular oedema
32	OS	6/15 (20/50)	6/9 (20/30)	Disruption of the macular pigment epithelium
Treated				
3	OS	6/150 (8/200)	NLP	Questionable final vision; secondary gain suspected
4	OS	1/66 (3/200)	HM	Macular atrophy
5	OS	1/100 (2/200)	1/100 (2/200)	Cataract and persistent macular oedema
6	OD	6/120 (20/400)	6/90 (20/300)	Persistent macular oedema
8	OS	6/15 (20/50)	1/66 (3/200)	Macular haemorrhage
9	OS	1/66 (3/200)	1/66 (3/200)	Peristent macular oedema
13	OS	6/21 (20/70)	LP	Retinal detachment
15	OS	1/40 (5/200)	6/120 (20/400)	Persistent macular oedema
17	OS	6/120 (20/400)	HM	Persistent macular oedema
23	OS	1/100 (2/200)	1/100 (2/200)	Macular hole
24	OS	1/40 (5/200)	1/40 (5/200)	Macular hole
25	OS	6/60 (20/200)	6/60 (20/200)	Disruption of the macular pigment epithelium
28	OD	1/200 (1/200)	HM	Peristent cystoid macular oedema
29		1/66 (3/200)	HM	Preretinal fibrosis
33		1/21 (9/200)	6/90 (20/300)	Macular photocoagulation scar

*NLP indicates no light perception; LP, light perception; and HM, hand motions.
†NVG indicates neovascular glaucoma.

viously in the involved eye. Another patient had bilateral occlusion within a month, and both eyes were included in the study. Two patients had total superior branch vein occlusion in their noninvolved eyes (see Table 4).

The persistence of oedema was the main cause of prolonged decreased vision. The average duration of macular oedema was longer in the treated group (13·0 months) than in the untreated group (11 months). The long duration of macular oedema and its sequelae were the main reasons for poor visual results in most of the eyes. This was especially true for the treated eyes. The duration of the oedema might have been reduced if we had administered photocoagulation within the temporal vascular arcades. All photocoagulation was outside the vascular arcades. All eyes except 1 developed CME prior to photocoagulation. This eye had a previous branch vein occlusion and had well-developed shunt vessels on the disc at the time of the central retinal vein occlusion.

On the average NVD was seen earlier in the treated than in the nontreated group. In 3 of the eyes it developed after photocoagulation. The NVD cleared faster in the treated eyes, but a small amount persisted in 2 treated eyes. No conclusion could be reached with respect to NVE because only 1 patient in each group developed it (see Table 4).

All 5 eyes in the nontreated group that developed rubeosis and NVG had large areas of retinal capillary obliteration (16·0 disc areas or more), as demonstrated by fundus fluorescein angiography. The remaining nontreated eyes had significantly smaller areas of retinal capillary obliteration (9·0 disc areas or less). Four of the treated patients had large areas of retinal capillary obliteration that were comparable to those of the eyes developing rubeosis and NVG. None of the eyes in the treated group, however, developed rubeosis or NVG.

The development of rubeosis may be directly related to the degree of retinal capillary obliteration. This may serve as a useful prognostic indicator as to which eyes have a high probability of developing rubeosis after central retinal vein occlusion. Eyes with large areas of retinal capillary obliteration can be treated early with panretinal photocoagulation, and the unfortunate sequelae of rubeosis and NVG may be prevented.

This is a small series of eyes, and the areas of capillary drop-out reported here provide only a relative indication of the degree of retinal hypoxia required to produce rubeosis and NVG. Additional studies on many more eyes will be required for any absolute determination to be made as to what amount of retinal capillary obliteration renders an eye susceptible to rubeosis and NVG. At present from the results of this study it would seem that eyes with 10 or more disc areas of retinal capillary obliteration would be at greater risk and should be considered for panretinal photocoagulation.

The progression of rubeosis to NVG was very rapid in the affected eyes. Neovascular glaucoma was clinically present an average of 93 days after the onset of central retinal vein occlusion, which was consistent with the classic presentation of the so-called 100-day glaucoma.

More than half of the involved eyes in our series that did not develop NVG had lower intraocular pressures than in the noninvolved eye for an average of greater than 6 months. This has been noted by others (Moore, 1922; Vannas and Raitta, 1970; Hayreh, *et al.*, 1978) as well, but no explanation is available at present. No relationship was found to the degree of retinal capillary drop-out or to any other known factors in the eyes of our series. If the noninvolved eye of a patient in our series had primary open-angle glaucoma, both eyes were treated for open-angle glaucoma. Eventually both eyes of each patient equalised their pressures to within 2 mmHg or less, including those being treated for glaucoma.

Panretinal photocoagulation is not without complications. Two patients of our series had a decrease or loss of useful vision as a result of treatment. These included 1 eye that developed a retinal detachment and an accidental photocoagulation of the macula of another eye. A macular haemorrhage that developed 4 weeks after treatment also may have been precipitated by photocoagulation. Iris burns were created inadvertently in 2 eyes and transient choroidal effusions resulted in 3 eyes. Caution must be exercised in the delivery of photocoagulation.

Dr Morton F. Goldberg provided valuable suggestions during the course of the study and critically reviewed the manuscript. Vijai K. Moses statistically analysed our data. Norbert Jednock, Jerry Sewell, Marlene Fishman, and Larry Seligman provided photographic assistance. Joyce G. Schwartz assisted with the preparation of the manuscript. Maxine Gere edited the manuscript.

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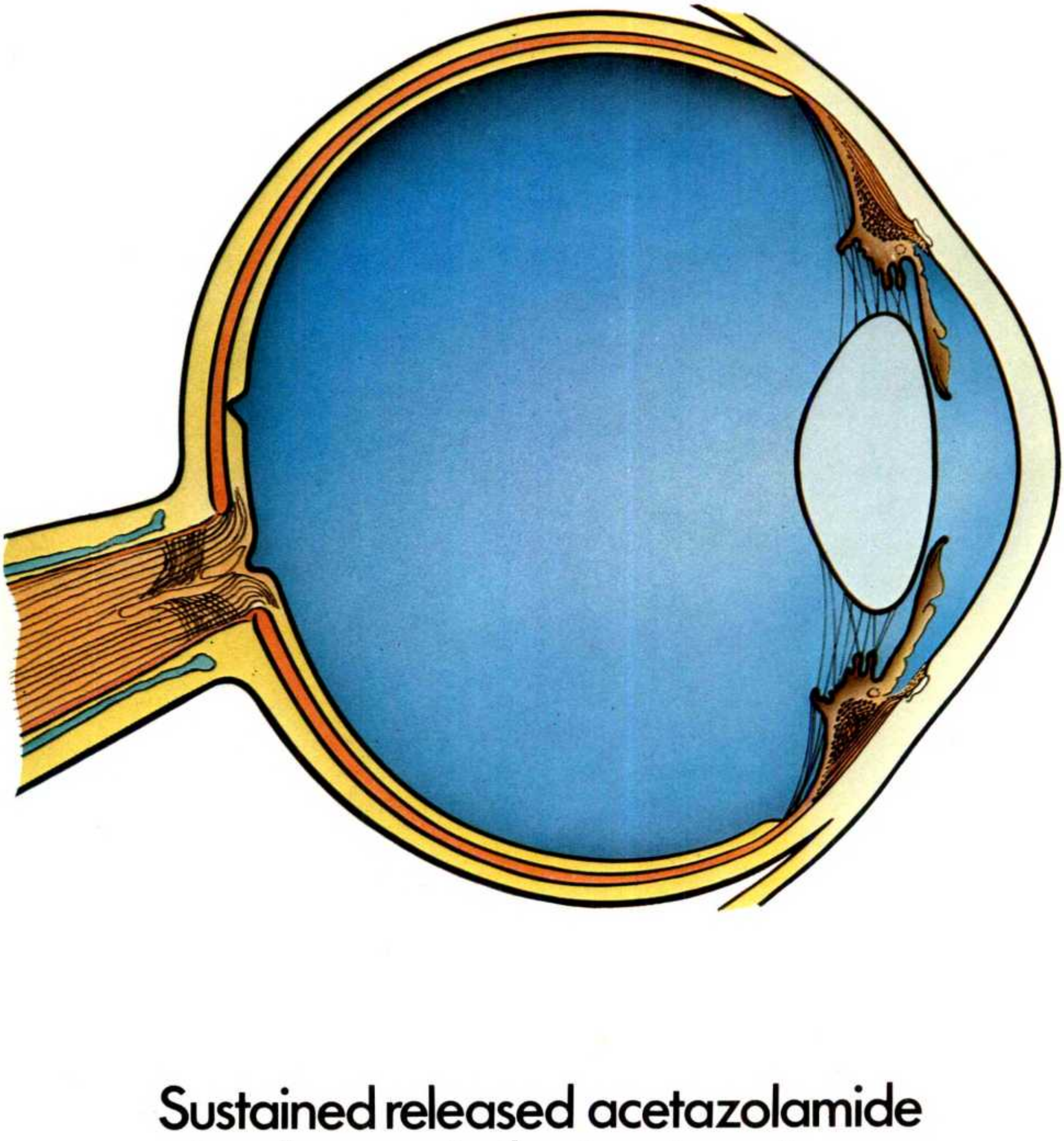
The circles of darkness

Diamox Sustets



Sustained released acetazolamide
therapy in the treatment
of glaucoma.

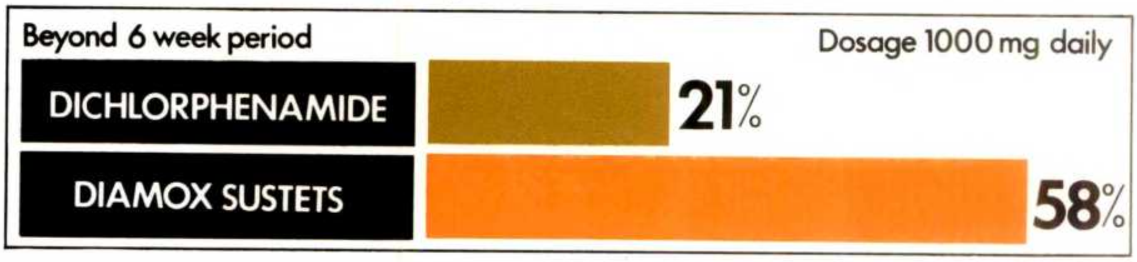
Diamox Sustets

a significant advance in patient tolerance

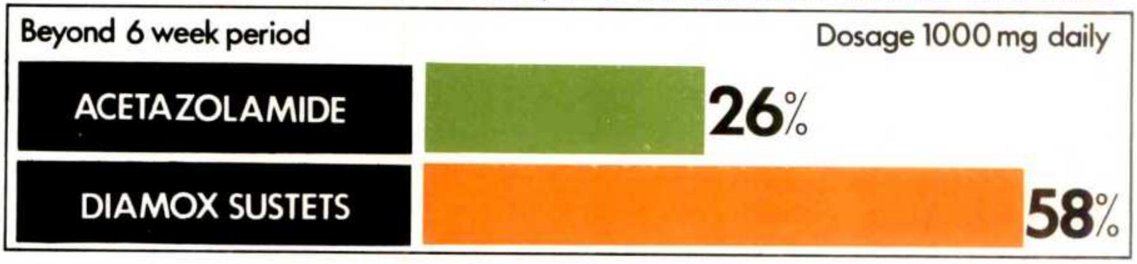
NEW EVIDENCE[6]

In a recent trial comparing glaucoma patients' acceptance to carbonic anhydrase inhibitors also acetazolamide tablets the following results were obtained:-

Patient tolerance of carbonic anhydrase inhibitors.



Patient tolerance of Diamox Sustets compared with standard acetazolamide tablets.



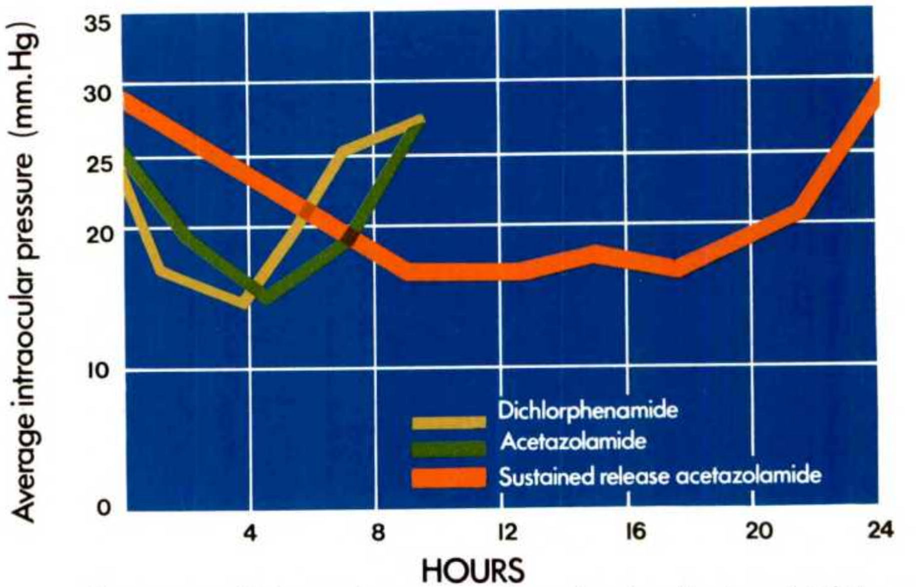
This trial supports previous studies confirming the exceptional patient tolerance with Diamox Sustets therapy.

- Diamox Sustets provide greater patient compliance with a simple b.d. dosage.

> ❝ Fifty-eight per cent of the patients could be expected to tolerate [Diamox Sustets] beyond six weeks. This is greater than any other agents.....it seems worthwhile to begin treatment with this drug at the dosage levels used in this study. ❞[6]
>
> (Dosage used–1 Diamox Sustet every 12 hours).

Diamox Sustets

longer action than other systemic therapies[4]



Response of intraocular pressure to carbonic anhydrase inhibitors

The sustained release form of Diamox has a far longer duration of action than any other systemic therapy.

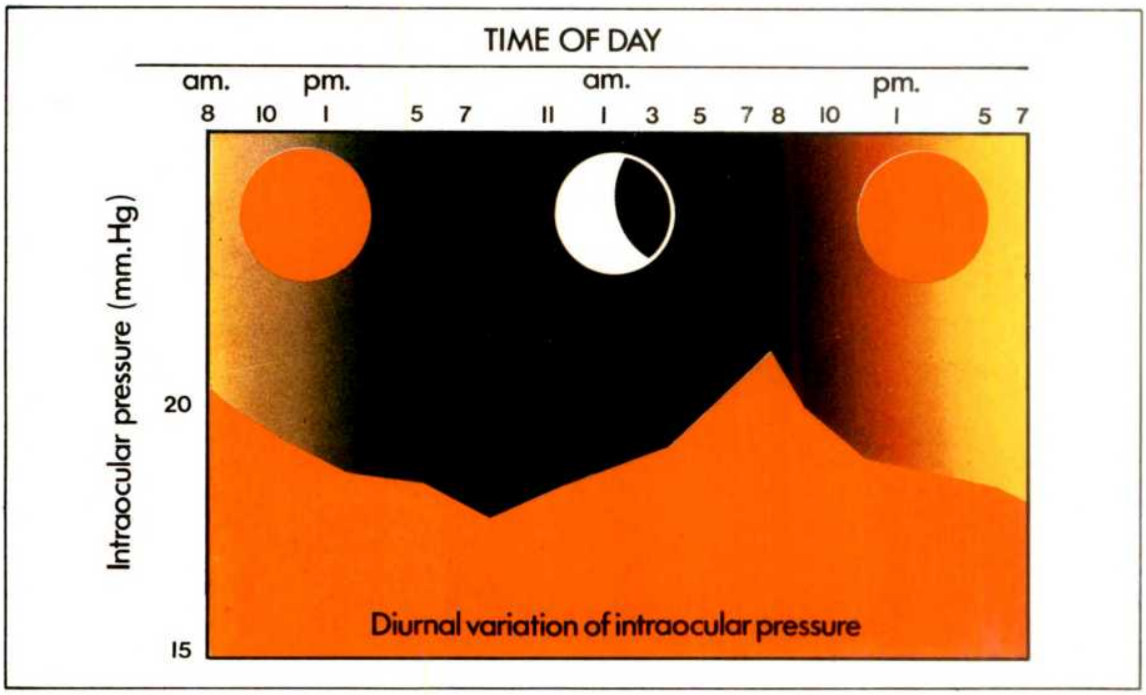
● longer action than pilocarpine

The effect of pilocarpine in intraocular pressure does not last more than six hours.

PILOCARPINE	6 HOURS[5]
DIAMOX SUSTETS	24 HOURS

Diamox Sustets

maximum control of intraocular pressure



24 hour variations in pressure[1]

It has long been known that the early morning pressure peak normally occurring just before and on waking is the most potentially destructive to the affected eye. The chart above shows an average diurnal-nocturnal variation in glaucoma.

Diamox has been shown[2] to reduce intraocular pressure by up to 60% and the sustained release form —Diamox Sustets—gives a true 24 hour duration of effect per capsule[3], providing a smooth control of intraocular pressure –and avoiding the necessity of the night time dose usually associated with glaucoma chemotherapy.

Diamox Sustets

Sustained release Diamox therapy

- smoother control of intraocular pressure.
- sustained blood levels with reduced peaks for lowered incidence of side effects.
- a simple b.d. dosage.

Presentation Each orange transparent capsule coded 'Lederle 4479' contains acetazolamide 500 mg formulated to release 125 mg immediately and 375 mg gradually over a six to eight hour period. **Uses** Diamox is an enzyme inihibitor and acts specifically on carbonic anhydrase which affects the reversible hydration of carbon dioxide and dehydration of carbonic acid in the kidney and other sites. The result is renal loss of HCO_3- ion which carries out sodium, water and potassium. **Indications** Glaucoma. **Dosage and administration** *Adults:* 1 Capsule at night and in the morning. The product is not intended for administration to children. **Contra-indications, warnings, etc** *Contra-indications:* Since Diamox Sustets may induce a mild acidosis, its use is contra-indicated in idiopathic renal hyperchloraemic acidosis. Because of the nature of its action, Diamox Sustets may be contra-indicated in conditions in which there is a known depletion of sodium and potassium at least until after successful preliminary medication with sodium and potassium salts. It is also contra-indicated in Addison's disease or all types of suprarenal gland failure.

Long-term administration is contra-indicated in patients with chronic noncongestive angle-closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intra-ocular pressure. *Precautions:* Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia. Less commonly, fatigue, excitement, gastro-intestinal upsets and increased polyuria have been reported. Disorientation has been observed in a few patients with oedema due to hepatic cirrhosis. Such cases should be under close supervision.

When Diamox Sustets is prescribed for long-term therapy, special precautions are advisable. The patient should be cautioned to report any unusual skin rash. Periodic blood counts are recommended. A precipitous drop in formed blood cell elements or the appearance of toxic skin manifestations should call for diminution or cessation of Diamox Sustets therapy. The transitory loss of hearing calls for immediate cessation of medication. *Side-effects:* Instances of flushing, thirst, headache, drowsiness, dizziness, fatigue, irritability, excitement, polydipsia and polyuria, paraesthesia of extremities and face, ataxia, hyperpnoea, and gastro-intestinal upsets such as anorexia and vomiting have been reported. These side-effects have normally disappeared during continued medication or upon diminution or cessation of Diamox Sustets therapy.

However, Diamox Sustets is a sulphonamide derivative and therefore some side-effects similar to those caused by sulphonamides have occasionally been reported. These include fever, agranulocytosis, thrombocytopenia, thrombocytopenic purpura, leukopenia, and aplastic anaemia, skin toxity, crystalluria, calculus formation, renal and ureteral colic and renal lesions.

Transient myopia has been reported. This condition invariably subsides upon diminution or discontinuence of the medication. *Overdosage:* No specific antidote. Supportive measures with correction of electrolyte and fluid balance. Force fluids. **Pharmaceutical precautions** Nil. **Legal category** POM. **Package quantities** Bottles of 30, 100 and 500. Code 4479. **Further information** Nil. **Product licence number** 0095/5074.

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Prognosis for rubeosis iridis following central retinal vein occlusion

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SUMMARY The records of 57 patients with recent central retinal vein occlusion were reviewed in order to predict the development of rubeosis iridis (RI) and neovascular glaucoma (NVG) from the initial clinical examination, colour fundus photographs, and fluorescein angiograms. Twelve patients (21 %) developed both RI and NVG, and this complication appeared to be correlated most significantly with clinical and fluoroangiographic evidence of severe retinal ischaemia. The correlation between RI and other findings was as follows: widespread capillary occlusion (86 % developed RI); absent perifoveal network (80 %); 10 or more cotton-wool spots (75 %); A-V transit time of greater than 20 seconds (75 %); severe large vessel leakage (31 %); and severe retinal oedema (60 %). Less significant correlation of RI was obtained with poor visual acuity and with associated systemic diseases. Factors of no statistical prognostic value included the patient's age, history, or evidence of pre-existing open-angle glaucoma, degree of fundus haemorrhage, capillary dilatation, disc oedema, disc capillary dilatation and leakage, leakage of small vessels in the posterior pole, and development of disc collateral vessels. Multivariate linear discriminant analysis of the data supported the above factors as being the variables that best predicted the development of RI, and a derived linear equation predicted 91 % of all patients studied who had central retinal vein occlusion and who developed rubeosis iridis.

Rubeosis iridis (RI) and neovascular glaucoma (NVG) are severe complications of central retinal vein occlusion (CRVO) which occur in 12% to 30% of all cases (Smith, 1961; Vannas, 1961; Laatikainen and Kohner, 1976). The stimulus for anterior segment neovascularisation is poorly understood but is thought to be related to severe retinal ischaemia (Smith, 1961; Ashton, 1961; Shilling and Kohner, 1976). Fluorescein angiography adds considerable information to the understanding of the pathophysiology of CRVO by enabling qualitative evaluation of the retinal vascular responses to an ischaemic lesion. These responses include retinal capillary nonperfusion, dilatation of small vessels, microaneurysm formation, and abnormal vascular permeability secondary to endothelial cell damage. Studies in diabetics (Laatikainen and Kohner, 1976; Kohner *et al.*, 1976) have suggested a relation between the development of fundus or iris neovascularisation and widespread areas of retinal capillary nonperfusion. A similar relation has been reported for branch vein occlusion (Kohner *et al.*, 1976; Sedney, 1976; Laatikainen and Blach, 1977) and CRVO (Laatikainen and Kohner, 1976; Hayreh, 1976, Kottow *et al.*, 1976; Laatikainen, 1977a).

Prognosticating this complication has become important, since recent studies (Sedney, 1976; May *et al.*, 1976; Laatikainen, 1977b) have reported that panretinal photocoagulation may be used to reverse or prevent iris neovascularisation after CRVO. It has been suggested, however, that treatment should be completed either early in the course of rubeosis, before extensive peripheral anterior synechiae are established, or prophylactically before clinical rubeosis is recognised. This obviously necessitates the early identification of those patients with CRVO who are at high risk of developing neovascular complications. This study was undertaken to extend previous studies (Laatikainen and Kohner, 1976; Laatikainen and Blach, 1977) in order to determine the features of either the initial clinical examination, the fluorescein angiogram, or both, that might be statistically correlated with the subsequent development of anterior segment neovascularisation.

Materials and methods

The records of patients with CRVO who had been referred to the Massachusetts Eye and Ear Infirmary Fluorescein Service were reviewed for development of clinically unequivocal rubeosis iridis, neovascular glaucoma, or both. Only patients with relatively 'fresh' vein occlusions were selected; patients with 'old' occlusions, either by history or by fundus criteria, were excluded. The duration of symptoms prior to the initial examination of the 57 patients included is shown in Table 1. Fifty-four cases were unilateral and 3 bilateral, in which a CRVO had occurred recently after an older occlusion in the fellow eye. The average age of the patients was 60 years, with a range of 23 to 93 years. All patients were followed up until resolution of the CRVO or until they developed clinically unequivocal rubeosis iridis or neovascular glaucoma. The average follow-up period of eyes that did not develop rubeosis was 10 months (range 4 to 36 months). Most patients received no treatment after initial evaluation; only a few were treated with antifibrinolytic agents, anticoagulants, or steroids.

Patients' records, which included stereo fundus photographs, stereo fundus fluorescein angiograms, and data from the initial and follow-up examinations, were reviewed for the following details: (1) history: duration and type of symptoms, age, associated systemic, ocular, or orbital disease; (2) initial ocular examination: visual acuity, intraocular pressure, afferent pupillary defect; fellow eye visual acuity, intraocular pressure, disc or field changes, and retinal pathology; (3) course: final visual acuity, time required for resolution of haemorrhages and oedema, development of macular cysts, disc collaterals, unequivocal iris neovascularisation (aberrant surface vessels visible on biomicroscopy), or neovascular glaucoma.

Table 1 *Duration of symptoms in patients with CRVO*

Duration of symptoms	*No. of patients (%)*
1 mo	29 (51)
2–3 mo	13 (23)
>3 mo	6 (11)
Undetermined length of time	5 (9)
Routine examination without symptoms	4 (7)

CRVO=central retinal vein occlusion.

For the purpose of this study the photographed retina of the involved eye was divided into 3 territories for evaluation of various areas: (1) macula: area within a 2-disc radius from the fovea; (2) posterior pole: disc and area within the major temporal vascular arcades, except for the macular area described above; (3) periphery: area peripheral to the disc and major temporal arcades. Colour stereo fundus photographs were used to assess the severity or extent of retinal haemorrhages, oedema, and cotton-wool spots within these 3 territories, and collateral disc vessels.

In each of the above territories the intraretinal, deep, superficial, and subhyaloid retinal haemorrhages were graded: none (0), mild (1), moderate (2), or severe (3) (the number in parentheses is the grade of severity for each variable that we included in the multivariate discriminant analysis; see 'Statistical analysis'). Retinal oedema was graded: none (0), mild (1), or severe (2), with notation of the formation of macular cysts (3). The number of cotton-wool spots was recorded, as well as their papillary, peripapillary, or peripheral location. Opticociliary veins were either present (1) or absent (0).

Stereo fluorescein angiograms were used to evaluate retinal capillary nonperfusion, capillary dilatation, and vascular permeability. In each of the 3 territories we evaluated the integrity of the retinal capillary bed during early dye transit as well as could be determined through and between the retinal haemorrhages. Even in cases with extensive haemorrhages ischaemic areas could be delineated with relative ease (Fig. 1). In the macular area, the perifoveal capillary arcade was described as present (0), broken (1), or absent (2) (no perfused capillaries within a one-disc radius of the fovea). In the posterior pole and periphery the total area of capillary nonperfusion was graded from no capillary occlusion (0) to scattered foci of occluded capillaries totalling less than 1 quadrant (1), 1 to 2 quadrants (2), or severe, contiguous occlusion totalling 3 to 4 quadrants (3). In each territory of the angiogram the total area of capillary dilatation or microaneurysm formation was estimated and graded: none (0), scattered foci totalling less than 1 quadrant (1), 1 to 2 quadrants (2), or 3 to 4 quadrants (3). Ischaemic damage to the vascular endothelium was determined by the degree of abnormal permeability observed in the small vessels (capillaries and venules) or the large veins in 2 retinal territories—the posterior retina (macula and posterior pole) and the peripheral retina. Permeability was graded: none (0), mild staining (1), mild leakage (2), or severe leakage (3). Forty fluorescein transits were timed, and the arteriovenous transit time was estimated, from the appearance of dye in the

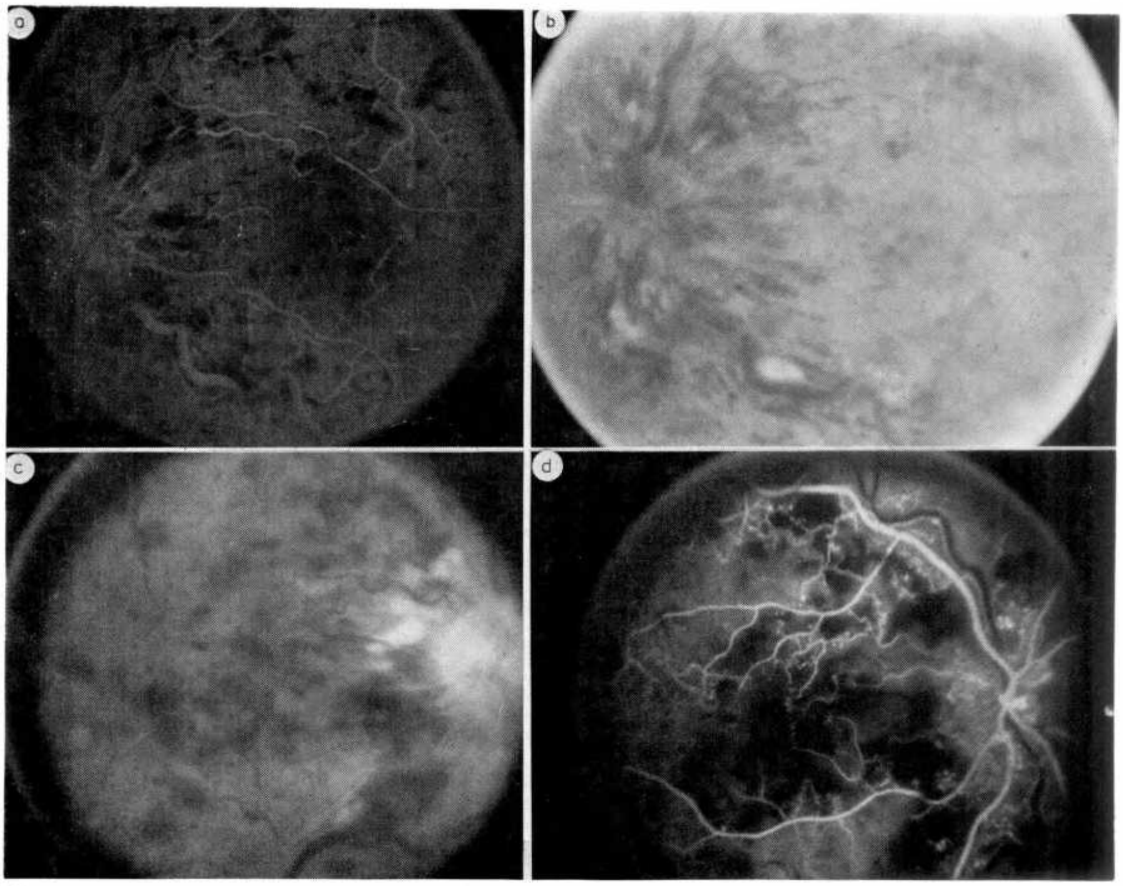

Fig. 1 *Fundus photograph and mid-capillary-transit fluorescein angiogram of patient with CRVO.* A, B: *Mild, scattered foci of capillary occlusion;* C, D: *Extensive capillary occlusion*

retinal arteries to the complete filling of the major central retinal veins.

STATISTICAL ANALYSIS

All of the collected data and their association with rubeosis iridis were subjected to statistical analysis by χ^2 tests for the resultant 3×2 or 4×2 tables. The data were also subjected to a computer analysis which derived a multivariate, linear, discriminant coefficient equation. This analysis evaluates the potential of each variable, alone and in combination with others, to predict which patients will develop rubeosis iridis as a complication of CRVO. The programme derives a linear equation of those variables that are the best predictors. A weighted coefficient, assigned to each variable, is multiplied by the graded severity of the variable: $X = K + C_1 (V_1) + C_2 (V_2) + C_3 (V_3) + \ldots + C_n (V_n)$ where K is a constant, $C_1 \ldots C_n$ are the weighted coefficients for the best-predicting variables, and $V_1 \ldots V_n$ are the graded values of the patient for each variable. The resultant discriminant score (X) indicates the tendency of that patient to develop rubeosis iridis. We can thus derive a weighted combination of the best-predicting variables which may serve better than any 1 variable alone to predict which patients will develop rubeosis iridis. A discriminant score was calculated for each patient by means of coefficients of the best-predicting variables derived by the programme along with their graded values (the parenthetical values described above).

Results

Rubeosis iridis developed in 12 of 57 patients (21%) with early CRVO within a period of 3 weeks to 7 months after the onset of symptoms (Table 2),

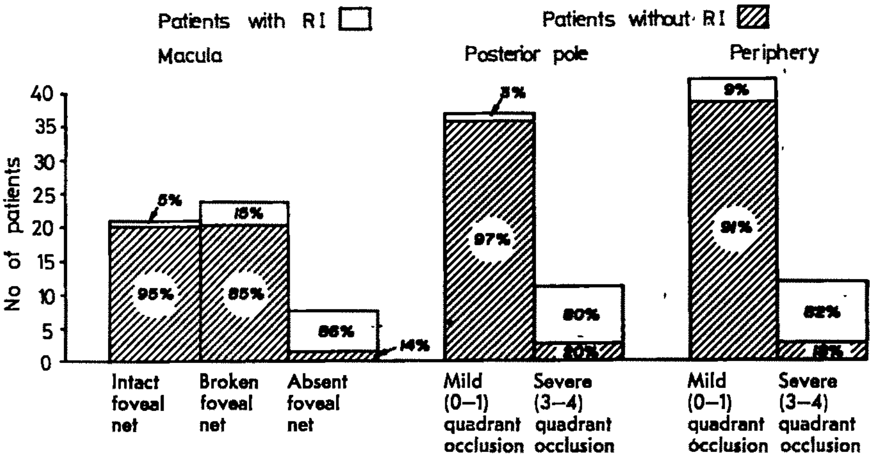

Fig. 2 *Correlation of rubeosis iridis (RI) with degree of retinal capillary occlusion seen on fluorescein angiogram following CRVO*

Table 2 *Interval between onset of symptoms and development of rubeosis in CRVO*

Interval (months)	*No. of patients*
<1	1
1–	2
2–	3
3–	3
4+	3
Total	12

CRVO=central retinal vein occlusion.

and in all these patients angle neovascularisation and glaucoma ensued. The development of rubeosis iridis was most significantly correlated with those features of the initial clinical examination and fluorescein angiogram that indicated severe retinal ischaemia. As shown in Fig. 2, rubeosis iridis correlated most directly with the extent of capillary nonperfusion that was observed on the fluorescein angiogram. Rubeosis developed in 80–86% of eyes with an absent parafoveal net of 3 to 4 quadrants of posterior pole or peripheral capillary occlusion, but appeared in only 3–9% of those with an intact parafoveal net and less than 1 quadrant of capillary occlusion. These results were significant, P <0·001 level. The view of the perifoveal arcade was sufficiently blocked by haemorrhage to prevent evaluation in 6 patients.

Less significant correlations were obtained for other indices of retinal ischaemia. Among patients with greater than 10 cotton-wool spots (CWS) rubeosis developed in 75% (Fig. 3), whereas the incidence was 24% in patients in whom less than 10 CWS were observed, and only 14% if no CWS were noted (P <0·001). Increased vascular permeability (Fig. 4) and retinal oedema (Fig. 5) were even less well correlated. Among patients with severe grades of leakage and oedema rubeosis iridis and neovascular glaucoma developed in 31–60%, but the incidence decreased to 4–10% in those with no leakage or mild staining of the vessel walls (P <0·05). A prolonged A-V transit of more than 20 seconds was associated with a significantly higher incidence of rubeosis iridis, 75%, whereas the condition developed in only 10% of those with a transit of less than 20 seconds (P <0·001; Fig. 6).

Although a significant correlation between the initial visual acuity and subsequent anterior segment neovascularisation was noted, this relationship was less marked than the previous indices. Rubeosis developed in 36% of the patients whose initial acuity was 6/60 (20/200) or worse, but arose in only 7% if the acuity was 6/30 (20/100) or better (P <0·01).

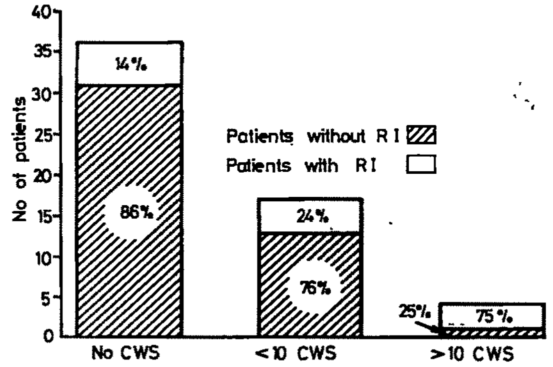

Fig. 3 *Correlation of rubeosis iridis (RI) with number of fundus cotton-wool spots (CWS) following CRVO*

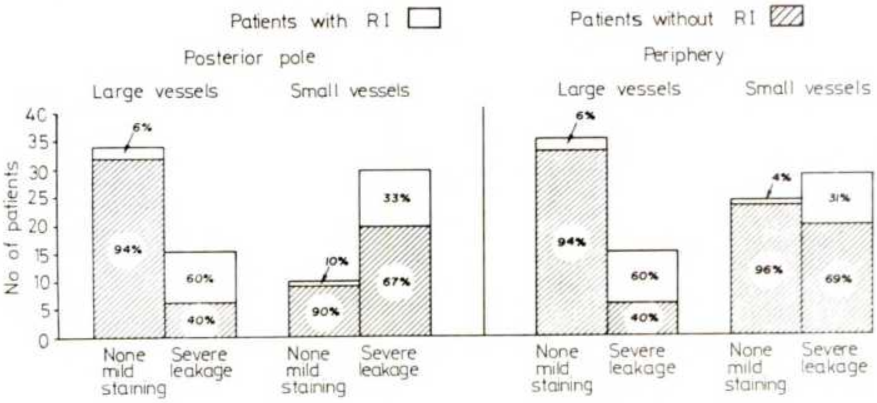

Fig. 4 *Correlation of rubeosis iridis (RI) with abnormal vascular permeability and leakage of fluorescein following CRVO*

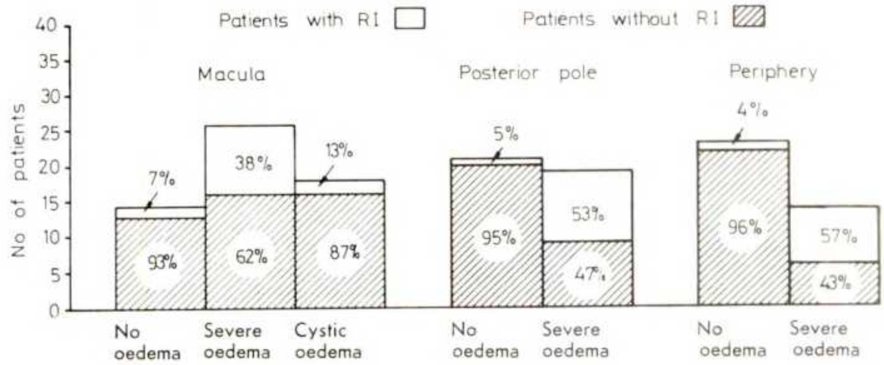

Fig. 5 *Correlation of rubeosis iridis (RI) with retinal oedema following CRVO*

Moderate or severe degrees of arterial, venous, or diabetic fellow-eye fundus abnormalities were not correlated with a statistically different prognosis (24%, 33%, and 20% developed RI respectively) than a normal fundus in the fellow eye (17% developed RI). Other factors which were studied but found to be of no statistical prognostic value included the following: the extent of fundus haemorrhage in the involved eye, the extent of capillary dilatation, the degree of disc oedema, disc capillary dilatation or leakage, leakage of small vessels in the posterior pole, and the presence of established disc collateral vessels.

Age was not correlated with neovascularisation; the average age of those with or without rubeosis was the same (63 ± 19 yr versus 59 ± 16 yr respectively). Furthermore, when patients were divided into young (<45 yr) and old (>45) age groups, there was no significant difference in the percentage of each group of patients (18% and 22%) in whom rubeosis developed.

A relatively small number of patients with rubeosis had associated systemic disease (Table 3), which included diabetes, hypertension, arthritis, arteritis, atherosclerotic cardiac and/or peripheral vascular disease, and hypercoagulable syndromes (including minor platelet dysfunctions and polycythaemia). Six patients had open-angle glaucoma (with a history of glaucoma or evidence of raised intraocular pressure (IOP) with pathological cupping in the fellow eye), and 6 patients had ocular

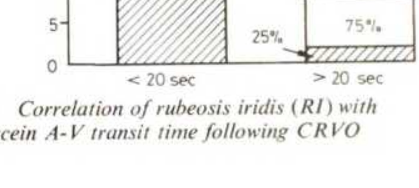

Fig. 6 *Correlation of rubeosis iridis (RI) with fluorescein A-V transit time following CRVO*

Table 3 *Associated diseases in patients with CRVO and rubeosis iridis*

Disease	*No. of patients with CRVO*	*No. of patients with RI*
None	13	1 (8%)
Hypertension	34	7 (21%)
Arthritis or arteritis	4	1 (25%)
Azotaemia	4	0 (0%)
Atherosclerotic cardiac/peripheral vascular disease	7	1 (14%)
Hypercoagulable/hyperviscosity syndrome	4	3 (75%)
Diabetes	9	2 (22%)
Primary open-angle glaucoma	6	2 (33%)
Ocular hypertension	6	0 (0%)

CRVO=central retinal vein occlusion. RI=rubeosis iridis.

hypertension (IOP >22 mmHg without pathological disc cupping). Taken individually, none of these conditions was statistically significant when compared with the incidence of rubeosis in the absence of systemic or ocular disease. Grouped together, however, the incidence of rubeosis occurring with any systemic or ocular disease (25%) was significant when compared with the incidence of rubeosis with CRVO without any associated systemic disease (8%) ($P < 0{\cdot}01$).

The condition of the perifoveal network and the observation of macular oedema on the initial fluorescein angiogram correlated well with the initial visual acuity as well as the prognosis for late acuity. This supports findings of previous studies (Laatikainen and Kohner, 1976; Kohner, 1976). If on the initial fluorescein angiogram the perifoveal capillary arcade was judged intact, then the initial acuity was related to the degree of cystic maculopathy. Patients with mild leakage achieved 6/12 (20/40) or better, whereas those with severe oedema, cysts, or both had 6/7·5 (20/50) to 6/60 (20/200) vision. If the perifoveal capillary arcade was broken or absent, the leakage and oedema were usually severe and the acuity 6/30 (20/100) or worse. In a few exceptional cases the leakage was mild, and the initial vision for a short period was surprisingly good (6/9 to 6/18) in spite of the broken arcade.

Macular oedema which was observed on the initial angiogram usually resolved during the course of the CRVO, often quickly if the ischaemia was mild and the leakage restricted to the capillaries and venules. If the perifoveal capillary arcade was intact, 84% of patients achieved a final acuity of 6/7·5 (20/30) or better. If, however, the initial angiogram showed the perifoveal net to be broken or absent, 87% of these patients had a final acuity of 6/60 (20/200) or worse, whether or not the macular oedema resolved.

From all the data gathered the linear discriminant analysis showed that, of all variables studied (except A-V transit time, which had incomplete data), those listed in Table 4 were best in predicting the development of rubeosis. For each patient the discriminant score was calculated according to the equation given in Materials and Methods; for example, for patient 13:

$$X = +0{\cdot}4423 + (0{\cdot}4128)\,(1) + (-0{\cdot}1072)\,(10) + (-0{\cdot}1041)\,(2) + (-0{\cdot}2265)\,(3) + 0{\cdot}2870\,(3) = -1{\cdot}7630.$$

A resultant negative value was correlated with a tendency to develop rubeosis; the greater the negative result, the stronger the tendency. The average discriminant score for the rubeosis patients was $-1{\cdot}58$, and for those without rubeosis $+0{\cdot}41$. Discriminant scores of 0 to $+2{\cdot}0$ were correlated with probabilities of 0·98 to 1·0 of not developing rubeosis; scores of 0 to $-3{\cdot}00$ were correlated with probabilities of 0·56 to 1·00 of developing rubeosis. By means of the discriminant scores for each patient and these probabilities the outcome for 52 of the 57 patients (91%) was correctly predicted by the discriminant function.

Discussion

The incidence of rubeosis iridis and neovascular glaucoma associated with CRVO in this study (21%) is in agreement with previous reports (Ashton, 1961; Smith, 1961; Kohner, 1976; Kohner *et al.*, 1976; Laatikainen and Kohner, 1976; Laatikainen and Blach, 1977). The results show that the complication of rubeosis iridis and neovascular glaucoma following CRVO can be predicted with a high degree of accuracy from features of the initial clinical examination and, more importantly, from

Table 4 *Discriminant coefficients of variables that best predict rubeosis following CRVO*

Variable	*Coefficient*
Constant = +0·4423	
Systemic disease	+0·4128
No. of cotton-wool spots	−0·1072
Macular nonperfusion	−0·8641
Posterior pole nonperfusion	−0·2265
Posterior pole small-vessel permeability	+0·2870

CRVO=central retinal vein occlusion.

findings of the initial fluorescein angiogram. These variables, summarised in Tables 5 and 6, are direct or indirect manifestations of an ischaemic infarct and support the concept that anterior segment neovascularisation is correlated with the degree or the extent of fundus ischaemia, or both. The strongest one-to-one correlation was with widespread capillary occlusion as seen on the fluorescein angiogram. Rubeosis iridis was correlated also with the funduscopic observation of cotton-wool spots, but less well than with the extent of capillary occlusion. This was probably because cotton-wool spots became individually less distinguishable as they became more numerous and confluent. Vascular permeability changes, as manifestations of ischaemic injury, showed less significant correlation with the development of rubeosis. This result might be secondary to the difficulty in localising and quantifying the leakage, but it is also possible that factors other than ischaemic damage to the endothelial wall may affect leakage and may not be related to retinal tissue hypoxia.

Table 5 *Factors associated with development of rubeosis iridis following CRVO*

Clinical features	*Patients developing RI, %*
Fluorescein angiogram	
Posterior pole or peripheral severe (3–4 quadrant) capillary occlusion	80
A-V transit time >20 s	75
Posterior pole or peripheral severe large vessel leakage	60
Posterior pole or peripheral severe small vessel leakage (excluding disc)	30
Funduscopy of involved eye	
10 cotton-wool spots	75
Posterior pole or peripheral severe retinal oedema	38–57
Visual acuity <6/60	36

CRVO = central retinal vein occlusion. RI = rubeosis iridis.

Table 6 *Factors that predict no development of rubeosis iridis following CRVO*

Clinical features	*Patients developing RI, %*
Fluorescein angiogram	
No significant areas of capillary occlusion	3–5
Minimal large or small vessel leakage	4–6
A-V transit time <20 s	10
Funduscopy of involved eye	
No retinal oedema (except disc)	7–10
No cotton-wool infarcts	14
Clinical presentation	
No evidence of systemic disease	8
Visual acuity >6/30	7

CRVO = central retinal vein occlusion. RI = rubeosis iridis.

Prolongation of the A-V transit time was correlated with the development of rubeosis, as observed by Laatikainen and Kohner (1976), but less well than the finding of capillary closure. This observation may be accounted for by the following: blood flow in the large vessels may be partially restored through recanalisation or the growth of collaterals, whereas capillary occlusion continues from ischaemic endothelial cell or pericyte swelling, or perhaps from pressure due to tissue turgor. Hence a prolonged A-V transit time may indicate only indirectly the severity of the ischaemic lesion.

We found that the appearance of disc collateral vessels was not necessarily correlated with the development of rubeosis. These vessels may develop in both ischaemic and non-ischaemic fundi. Even if established, these collaterals may not be adequate to improve the circulation significantly and affect tissue hypoxia. We observed, as did Hayreh (1976), that the fluorescein filling of large retinal vessels was often extremely slowed, in spite of established disc collateral vessels.

Areas of dilated capillaries are observed in fluorescein angiograms as a result of venous obstruction. However, the extent of dilated capillaries was not related to the development of rubeosis iridis in these patients. The area of dilated capillaries was much reduced in eyes with CRVO and severe retinal ischaemia, because of capillary closure over widespread areas.

Visual acuity was a poor predictor of the development of rubeosis iridis, because in the early course of CRVO, as reported also by Laatikainen and Kohner (1976) and Laatikainen (1977a, b), vision was decreased owing to macular oedema as well as perifoveal capillary occlusion (ischaemia). We observed also that perifoveal capillary ischaemia did not necessarily accompany posterior pole or peripheral retinal capillary ischaemia. Occasionally we examined angiograms of patients who had an intact perifoveal capillary arcade with fairly extensive peripheral capillary occlusion. However, the reverse was more often the case: frequently the macula was observed to have excessive capillary loss while the rest of the fundus was minimally affected. This predilection or peculiar sensitivity of the posterior pole to ischaemic injury has been noted by Hayreh (1976) and may perhaps be explained by the higher density of photoreceptors and neural elements in the posterior fundus, which cause this area to have higher oxygen requirements, or perhaps by different haemodynamics within different segments of the fundus.

In this study a CRVO associated with systemic, orbital, or ocular disease was correlated with a significantly increased risk of developing anterior segment neovascularisation. However, none of the associated diseases alone showed a statistically significant difference from the cases of rubeosis with no associated disease. This seems to be contrary to the impression of others that rubeosis occurs more frequently in CRVO patients with primary glaucoma or systemic disease (Vannas, 1961; Kottow *et al.*, 1976). Our observation that age was not significantly correlated with rubeosis iridis is also contrary to findings by Vannas (1961) and Kottow *et al.*, (1976), but the increased number of elderly patients having rubeosis with CRVO in this study merely reflected the increased incidence of CRVO in the elderly. This result, however, could be caused by an unrepresentative sample composed of the more severe CRVO patients referred to the Fluorescein Service.

In a previous study of CRVO by Laatikainen and Kohner (1976) it was suggested that a fluorescein angiogram taken 3 months after the occlusion was more accurate in evaluating perifoveal capillary net integrity than the initial angiogram or one taken within 1 month of the onset of symptoms. This was because of progressive deterioration (increased area of capillary occlusion) noted in follow-up angiograms of a few patients. Progression of the ischaemia, if common in CRVO cases, would prohibit early prognostication for rubeosis iridis. To evaluate this we reviewed follow-up fluorescein angiograms taken within 2 to 5 months in 15 patients in whom the initial angiogram was taken within 1 month of the onset of symptoms. The follow-up angiogram in 12 patients did not change significantly; the remaining 3 (20%) showed significant progression or worsening of capillary occlusion, dilatation, and leakage. In 1 of these patients, who had no ischaemia initially, we found scattered foci of capillary occlusion over less than 1 total quadrant. In the second patient, with no initial ischaemia, moderately severe 3-quadrant ischaemia was seen. The third patient, with patchy capillary occlusion, later showed severe confluent occlusion. However, rubeosis iridis developed in none of these 3. There was no particular feature of the initial history, ocular examination, or fluorescein angiogram that distinguished these patients from those who showed no progressive deterioration.

These results suggest that progressive ischaemic deterioration may occur in CRVO, but that the initial fluorescein angiogram and examination are accurate for most cases in prognosticating the complication of anterior segment neovascularisation. If, however, clinical findings suggest a progression of ischaemia, then perhaps angiography should be repeated. From reviewing these 15 angiograms we agree, however, with Laatikainen and Kohner (1976) that, for the purpose of prognosticating the final visual acuity in CRVO, the 3-month angiogram may be more accurate than the initial angiogram taken within 1 month of the onset of symptoms.

In conclusion, this study has shown that certain features of the initial clinical examination and, more particularly, of the initial fluorescein angiogram which indicate severe retinal ischaemia can prognosticate the development of anterior segment neovascularisation after CRVO. If capillary occlusion over 3 to 4 quadrants is recognised on the fluorescein angiogram, rubeosis iridis will develop in 80–86% of these patients, but rubeosis will develop in only 3–9% if minimal occlusion is observed. These extremes, however, represent only a small segment of all CRVO cases. If a discriminant score is calculated utilising capillary occlusion in combination with the other variables that also indicate retinal ischaemia, then up to 91% of all CRVOs might be accurately prognosticated.

Herbert Kayne performed statistical analysis and S. Flavia Blackwell provided editorial assistance.

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Metastatic tapioca iris melanoma

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SUMMARY A case of metastatic tapioca melanoma of the iris in a 12-year-old girl is reported. The patient had heterochromia, a red painful eye, and was treated for iritis with secondary glaucoma. In the course of 5 months iris lesions with the clinical appearance of tapioca pudding developed, and biopsy disclosed a melanoma. The eye was immediately enucleated, and pathological examination showed a melanoma with predominantly epithelioid-type cells which had infiltrated the angle, the posterior chamber, and the surgical wounds. Conjunctival extension was noted 10 months after enucleation, and regional lymph node metastases were found 4 months later. Previously reported cases are reviewed and compared with the present case.

Although melanomas are the commonest primary iris tumour (Ashton, 1964), they constitute only a small percentage of uveal neoplasms (Hogan and Zimmerman, 1962; Yanoff and Fine, 1975). Tapioca melanomas of the iris are rarer still, and there is no report of such tumours with epithelioid-type cells. Tapioca melanomas have a distinct clinical presentation and should be considered in the differential diagnosis of iris nodules (Shields *et al.*, 1976). In the past such tumours have been detected mainly between the second and third decades, with an average age of 29 years. All patients were Caucasians, and there was no sex predilection.

This paper reports an iris melanoma in a 12-year-old girl with the following interesting clinicopathologic features: an appearance like tapioca pudding on clinical examination, epithelioid-type melanoma cells on histopathogical examination, and extension of tumour to conjunctiva and regional lymph nodes.

Case report

A 12-year-old white girl was first seen by an ophthalmologist in December 1975 for a red and painful condition of the left eye of 2 weeks' duration. Findings included 'severe iritis' and raised intraocular pressure (40 to 50 mmHg by applanation tonometry). The right eye was normal and remained so throughout the course of the disease. A diagnosis of iritis with secondary glaucoma was made, and the patient was given mydriatics, topical and systemic steroids, and acetazolamide. Despite treatment, the eye remained inflamed, and the intraocular pressure fluctuated at 30 to 40 mmHg.

In February 1976 the patient was seen in consultation and findings in the left eye included: decreased vision (6/9); raised intraocular pressure (34 mmHg by applanation tonometry); small keratic precipitates, flare, and cell reaction (2 to 3+) in the anterior chamber; increased iris pigmentation; pigment on the lens capsule; and extensive pigmentation in the trabecular meshwork. The optic disc was normal (cup/disc ratio 0·4). Skin tests for toxoplasmosis and histoplasmosis, purified protein derivative, streptokinase-streptodornase, and candida gave normal results. The patient was diagnosed as having an idiopathic recalcitrant iritis. Over the next 3 months her left eye remained inflamed with intraocular pressures at 30 to 40 mmHg.

On 3 May 1976 (5 months after onset) visual acuity in the left eye was 6/24, and she had a 1 to 2+ flare and cell reaction in the anterior chamber. The pupil was dilated and nonreactive; the iris showed marked stromal atrophy with nodular elevations, which were particularly notable at 6 o'clock. The lens was covered anteriorly with deposits of pigment and 'inflammatory' cells. The anterior vitreous was free of cellular reaction. A glaucomatous cup was noted (cup/disc ratio 0·8), and the intraocular pressure was again raised (42 mmHg by applanation tonometry). At this time the differential diagnosis included malignancy (melanoma, lymphoma, or leukaemia), granulomatous uveitis (sarcoidosis, tuberculosis, and coccidioidomycosis), and xantho-

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granuloma. An iris biopsy and aqueous humour cultures were recommended. The aqueous humour cultures were negative for bacteria and fungi.

On 11 May 1976 she underwent a filtering procedure, an iris biopsy superiorly, and a biopsy of the peripheral iris inferiorly. Both biopsies showed atypical melanocytes, forming plaques on the anterior iris surface and within the stroma. Delicate blood vessels within the surface plaques and rare chronic inflammatory cells also were noted (Fig. 1). The pathological diagnosis was malignant melanoma. One week after the glaucoma operation, with the patient on steroids and antibiotics, the eye remained quiescent with pressures ranging between 12 and 15 mmHg by applanation tonometry.

In June 1976 the patient's condition deteriorated, her visual acuity dropping from 6/24 to hand motion. In spite of acetazolamide the intraocular pressure rose from 18 mmHg to over 40 mmHg. Keratic precipitates were noted on the corneal endothelium, and white flocculent material appeared on the anterior lens surface and in the inferior angle. Blood vessels extended into the whitish angle mass.

In July 1976 the patient complained of left orbital pain, nausea, and vomiting. Her visual acuity then was hand motion and her visual field was contracted. Her intraocular pressure was 40 mmHg, and the cornea was diffusely oedematous, with epithelial bedewing. The anterior chamber was deep. Severe flare and cellular reaction were noted, and a nodular mass filled the inferior angle. The pupil was nonreactive, dilated, and oval-shaped, with retraction of the iris at 12 and 6 o'clock. The anterior lens capsule was covered with flocculent debris; the

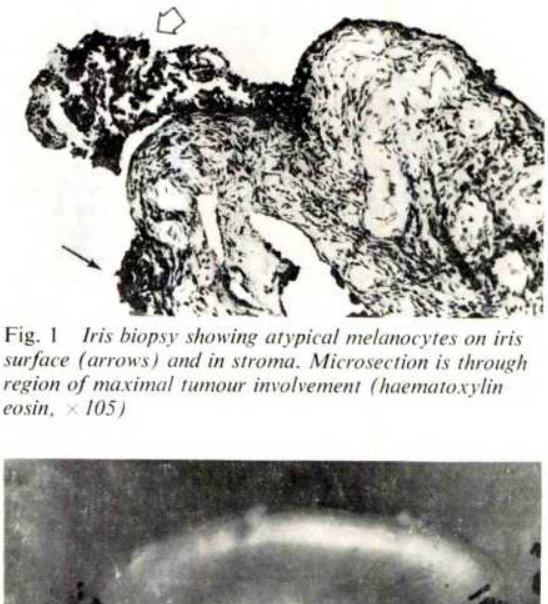

Fig. 1 *Iris biopsy showing atypical melanocytes on iris surface (arrows) and in stroma. Microsection is through region of maximal tumour involvement (haematoxylin eosin, × 105)*

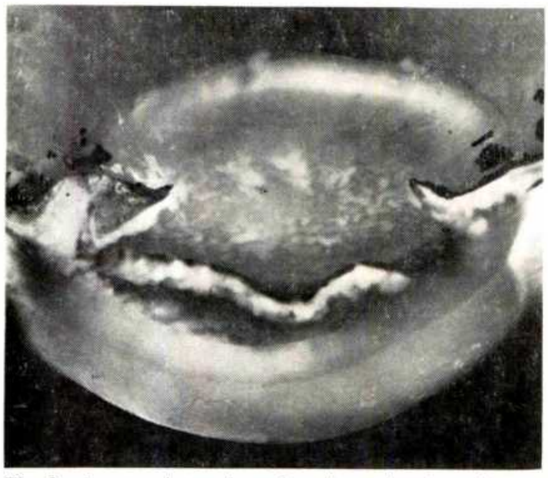

Fig. 2 *Large calotte of enucleated eye showing white confluent nodules coating both the anterior iris and lens surfaces*

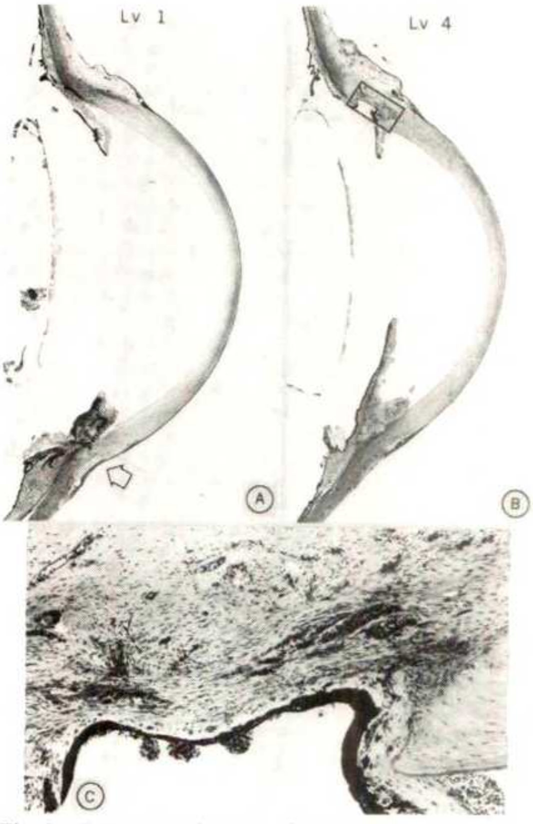

Fig. 3 *Tumour involvement of surgical wounds in vertically sectioned enucleated eye.* (A) *Level 1 shows the inferior iris biopsy wound (arrow) with extensive iris and ciliary body tumour.* (B) *Level 4 shows wound of filtering procedure (boxed area) and in* (C) *tumour infiltrating the superior wound*
*((*A) *Haematoxylin eosin, × 4;* (B) *Haematoxylin eosin, × 4;* (C) *Haematoxylin eosin, × 90)*

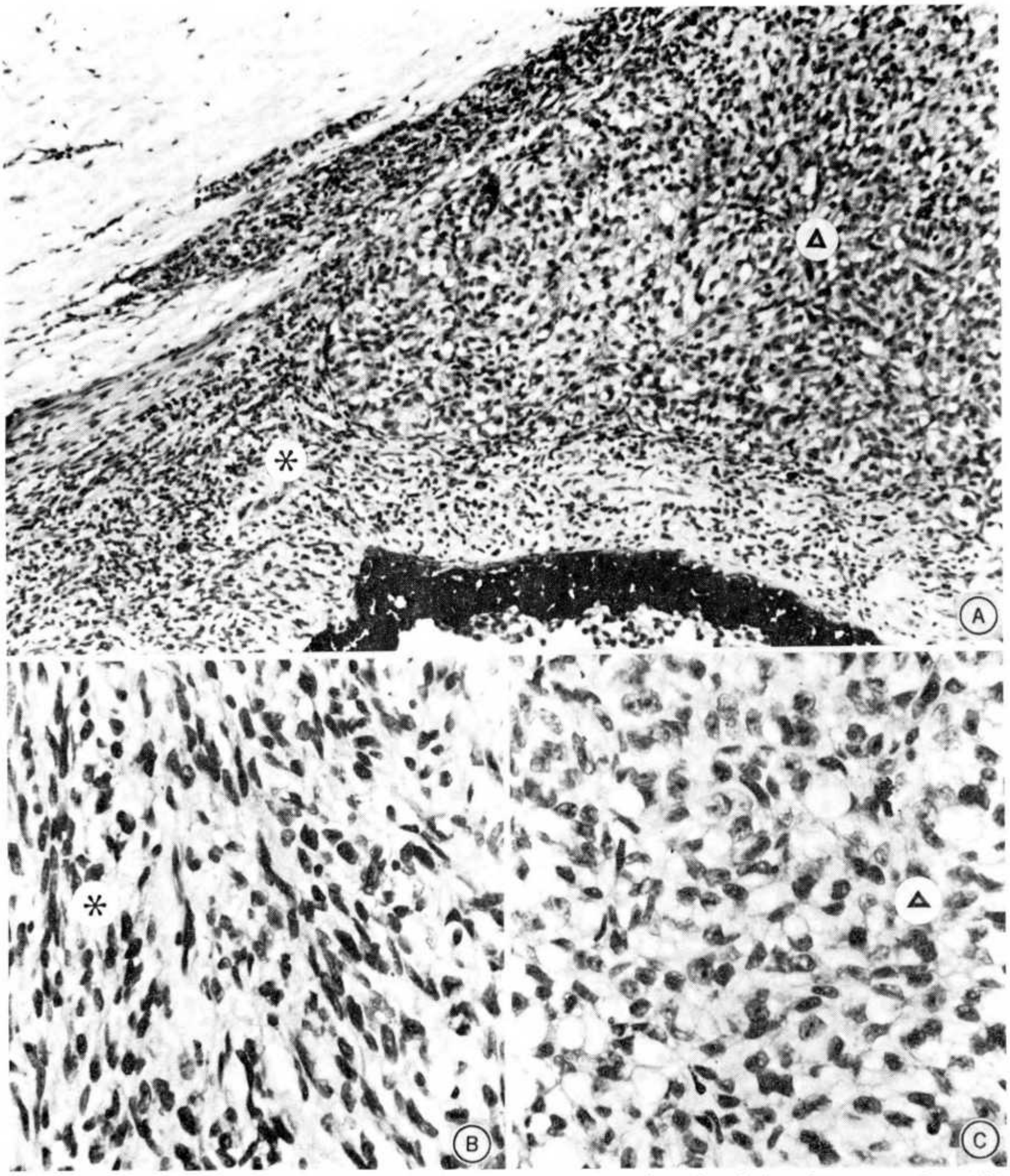

Fig. 4 *Tumour cytological variations.* (A) *Tumour fills angle recess (triangle), ciliary body and iris stroma (asterisk), and both the trabecular meshwork and Schlemm's canal.* (B) *Tumour in stroma is virtually completely composed of spindle cells.* (C) *Epithelioid cells are preponderant in anterior chamber.* (A) *Haematoxylin eosin,* ×*320;* (B) *Haematoxylin eosin,* ×*630;* (C) *Haematoxylin eosin,* ×*630*

fundus could not be visualised. There was ciliary injection and conjunctival hyperaemia. Gonioscopy showed a small, nodular, tan mass extending throughout the inferior angle. The eye was enucleated on 22 July 1976.

PATHOLOGICAL FINDINGS

Macroscopic eye examination showed an irregular pupil with defects both superiorly and inferiorly, and healing limbal wounds at 6 and 12 o'clock. On vertical sectioning nasal to the optic nerve there was a flocculent white 'exudate' partly filling the anterior chamber, coating the iris and lens, clogging the angles, and extending around an otherwise normal lens into the posterior chamber (Fig. 2). Anterior synechiae were noted at 11 o'clock. The optic disc showed a cup/disc ratio of 0.7. The vitreous was minimally hazy anteriorly but not invaded by tumour.

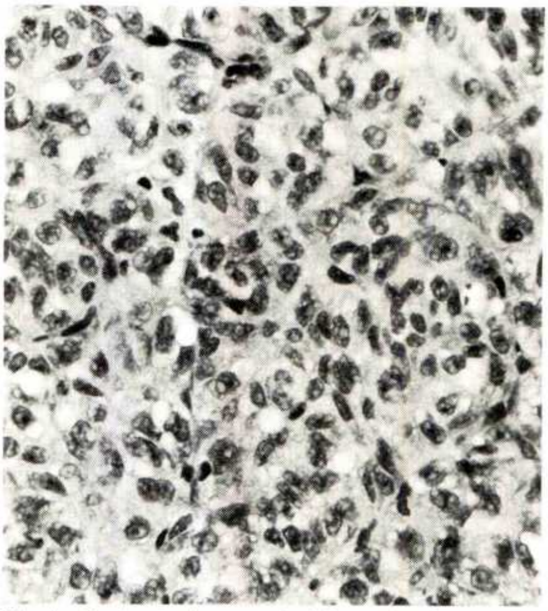

Fig. 5 *Conjunctival metastasis (12 months after enucleation), showing principally epithelioid cells (haematoxylin eosin, × 550)*

Microscopic examination showed both superior and inferior wounds, with a prominent iris mass inferiorly (Fig. 3). The tumour was minimally pigmented. Tumour cells were found in the trabecular meshwork around a few aqueous veins (Fig. 4), on the anterior lens surface, and in the anterior and posterior chambers. The iris stroma was primarily invaded by spindle-type melanoma cells, while the anterior chamber and its angle contained mainly epithelioid cells (Fig. 4). Occasional mononuclear inflammatory cells were found within the tumour. There was no extraocular extension, although both healing limbal wounds contained focal areas of tumour cells. The vitreous was free of tumour cells. The optic cup was markedly enlarged, and the lamina cribrosa was bowed posteriorly.

SUBSEQUENT CLINICAL FOLLOW-UP

In September 1976 an investigation for metastases was negative. In May 1977 (10 months after enucleation) a cyst-like lesion was noted along the conjunctival incision. Biopsy of this region revealed melanoma containing principally epithelioid-type cells (Fig. 5). Exenteration of the left orbit was advised but refused by the parents. In July 1977 (1 year after enucleation) a repeat investigation for

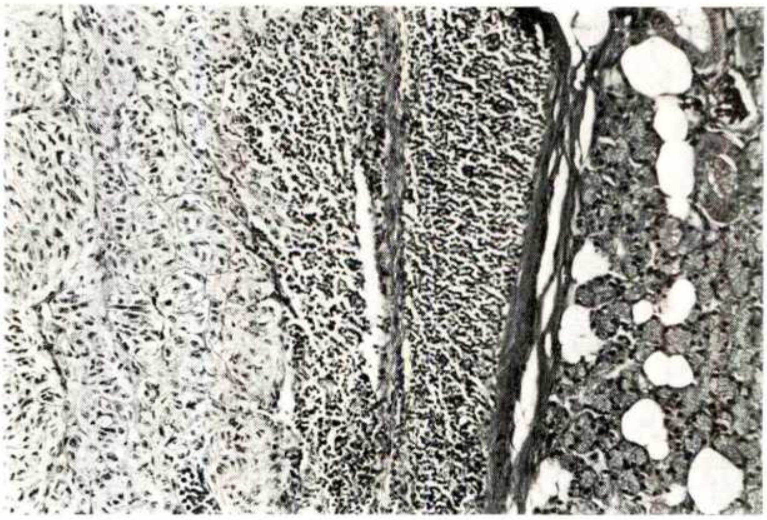

Fig. 6 *Parotid gland metastasis (14 months after enucleation). Section shows parotid gland (on right) with adjacent lymph node containing metastatic melanoma, which is largely epithelioid (haematoxylin eosin, × 115)*

metastases failed to reveal any evidence of distant spread. On 7 September 1977 (14 months after enucleation) an enlarged left preauricular lymph node was noted, the node being fixed to the underlying structures, not tender, and measuring 20× 30 mm. The left upper anterior cervical lymph node was enlarged also. Two weeks later a left partial parotidectomy was done with left radical neck dissection. Wide excision of the conjunctiva overlying the orbital implant was also performed. Histopathological examination of the excised conjunctiva showed a small focus of tumour cells and lymphocytes, but the surgical margins were free of tumour. One lymph node in the partly exised parotid gland was heavily infiltrated by epithelioid tumour cells (Fig. 6). All cervical lymph nodes were free of malignant cells.

Discussion

The first description of tapioca melanoma was given by Reese *et al.* (1972), who used the term because of the clinical resemblance of the tumour to tapioca pudding. Subsequently this lesion has been reported only rarely (Jarrett *et al.*, 1966; Wilson *et al.*, 1976). On comparison with previously reported cases (Table 1), that reported here is unique mainly because of the presence of epithelioid-type cells and because of remote metastases.

Table 1 *Clinical and pathological features of tapioca melanomas of the iris* compared with present case*

	*Previous cases**	*Present case*
Age (in years)	7, 21, 21, 21, 25, 27, 31, 34, 36, 38, 48	12
Sex: Female	6 of 11	Female
Male	5 of 11	—
Race	All white	White
Right eye	6 of 11	—
Left eye	5 of 11	1
Position†	7 of 11 inferior or inferotemporal quadrant	Inferior
No. of lesions	5 of 11 had 1 lesion 6 of 11 multicentric	— Multicentric
Shape	All nodular	Nodular
Pigmentation	8 of 11 little or none	Minimal
Cell type	All spindle	Epithelioid (predominant)
Ocular tension	Elevated in 4 of 11	Elevated

* Eleven total previously reported cases. † Position of largest or only nodule

Table 2 *Clinical management and survival of patients with tapioca melanoma of the iris*

Procedure	*Number of patients*	*Follow-up period(s)**
Preliminary iridectomy followed by enucleation	1‡, 3§	11 years, 11 years, 8 years (no follow-up on 1)
Enucleation only	1§	15 months
Iridectomy only	3§	19 months, 8 months, 6 years
Iridocyclectomy and photocoagulation	1‖	5 years
Iridectomy followed by enucleation and by lymph node dissection	1†	14 months
No surgical procedures	2§	No follow-up

* All patients have no recurrences and no evidence of metastasis. † Present case. ‡ Jarrett *et al.* (1966). § Reese *et al.* (1972). ‖ Wilson *et al.* (1976)

Few iris melanomas contained epithelioid-type cells (Richardson, 1948; Cleasby, 1958; Ashton, 1964; Roy, 1967), whereas all previously reported tapioca iris melanomas contained spindle-type cells (Jarrett *et al.*, 1966; Reese *et al.*, 1972; Wilson *et al.*, 1976). Topioca iris melanomas were always nodular and multicentric, most often inferior, and in some patients associated with a raised intraocular pressure. Although their surgical management differed and one-half underwent enucleation, all had a favourable outcome (Table 2). Follow-ups of 2 months to 11 years in those patients who had a surgical intervention revealed no local recurrence, and none of the remainder were complicated by metastases. Thus it is likely that both the epithelioid cell predominance and the biological aggressiveness of this neoplasm contributed to the systemic metastases. Finally, it should be stressed that the diagnosis of malignant iris melanoma should always be entertained in cases of unilateral iritis or glaucoma that are resistant to conventional treatment. The present patient is alive and free of detectable tumour metastases 14 months after invasion of lymph nodes and 28 months after enucleation.

This investigation was supported in part by Public Health Service research grants EY 00725 and EY 00331 from the National Institute of Health and the National Eye Institute and was performed during the period of special fellowship (Dr Zakka, Adelaide Stein Miller research fellow in ophthalmic pathology).

Follow-up data were furnished by R. Sloan Wilson, MD, and F. A. Jakobiec, MD.

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Microcysts of the human iris pigment epithelium

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SUMMARY Microcysts of the iris pigment epithelium have been described in association with diabetes mellitus, systemic mucopolysaccharidoses, Menkes's syndrome, and in neonates. Our study covers 68 cases obtained at necropsy. We specifically examined the iris pigment epithelium for vacuolation. We found that microcysts are more widespread than previously thought. In our series 57·3% of the cases reviewed by the light microscope showed microcysts. Of interest was the relationship of malignant neoplasm to iris pigment epithelium microcyst: 69·4% of cases with malignancy showed microcyst, whereas only 30% of the cases without neoplasms showed microcysts. Patients treated with exogenous steroid also had a raised incidence of microcysts.

The pigment epithelium of the iris is composed of a double layer of well-differentiated neuroepithelial cells. The cells of the anterior epithelial layer have a muscular basal portion whose elements comprise the dilator muscle, and a pigmented, epithelial apical portion. Those of the posterior layer are varied in size and shape and heavily pigmented. By light microscopy the iris pigment epithelium appears as a dark layer in which intracellular details are hidden by the heavy aggregation of melanin granules. Normally there are no obvious cysts within the iris pigment epithelial cells. However, in a number of conditions alterations of the iris pigment epithelium characterised as vesicles, vacuoles, oedema, or microcysts are found. We prefer the term microcyst(s) for this appearance. This report demonstrates that microcysts of the iris pigment epithelium (MIPE) are more frequent than previously reported, and that they may be associated with a number of disorders including neoplasms and may be induced by corticosteroid administration. We also show that the appearance of microcysts by light microscopy is dependent on the thickness of the histological section.

Materials and methods

This was a retrospective study of eyes obtained at necropsy during a 3-year period. The eyes were enucleated and fixed in formalin. They were then processed in the usual manner and embedded in paraffin. Sections 9 µm thick were cut and stained with haematoxylin and eosin. Eyes with extensive autolytic changes or those with a damaged iris pigment epithelium were excluded. Sixty-eight eyes were found suitable for this study. Particular attention was paid to the appearance of the iris pigment epithelium and it was specifically examined for the presence of microcysts. In several instances in which microcysts were noted the block was recut at 15 µm and the thicker section examined.

In all cases the patient's record was reviewed for the pathological diagnosis at the time of death as well as for the medical treatment that had been given during life. The ages of the subjects ranged from 42 to 87 with a mean age of 63.

Results

Thirty-nine cases showed definite microcysts and 29 did not (Table 1). Neoplasms of various kinds were the most frequent condition in which microcysts were noted, but they were also found in association with many other disorders. Eight out of 11 patients on high-dosage systemic steroids had evidence of microcysts; 5 of these patients had died of malignant diseases. The microcysts varied from a few cysts in several cells, to many cysts in most or all iris pigment epithelial cells (Figs. 1, 2, 3).

Sections cut at 15 µm or greater often failed to show the presence of microcysts that were readily visible at 9 µm (Figs. 4, 5).

Discussion

According to Duke-Elder (1966) Becker made the first reference to vacuolisation of the iris pigment

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Table 1 *Results of the present study*

Diagnosis	*Number of eyes MIPE present*	*Number of eyes MIPE absent*
Malignancy	25	11
Adenocarcinoma, G.	8 (1)	–
Carcinoma, lung	3	4
Carcinoma, breast	3	1
Adenocarcinoma, pancreas	1	–
Adenocarcinoma, prostate	1	–
Carcinoma, epidermoid	1	–
Papillary carcinoma, bladder	–	1
Carcinoma, penis	–	1
Adenocarcinoma, gall bladder	–	1
Adenocarcinoma, metastatic	–	1
Melanoma (metastatic)	1	–
Krukenberg tumour	1	–
Astrocytoma	–	1 (1)
Hodgkin's disease	2 (1)	
Lymphosarcoma	1 (1)	–
Recticulum cell sarcoma	1 (1)	–
Acute lymphocytic leukaemia	1	–
Histiocytosis	1 (1)	1
Renal failure	2 (1)	4
Cerebrovascular accident	2 (1)	–
Diabetes mellitus	2	1
Neonate with patent ductus	2	1
Pneumonia	1	–
Arteriosclerotic heart disease	1	2
Systemic lupus erythematosus	1	1 (1)
Cirrhosis	1	–
Gastrointestinal bleeding	1 (1)	1 (1)
Sepsis	1	–
Cardiopulmonary arrest	–	2
Jakob-Creutzfeld disease	–	1
Bacterial endocarditis	–	1
Lactic acidosis	–	1
Cockayne's syndrome	–	1
Viral hepatitis	–	1
Multiple myeloma	–	1
Total	39 (57·3%)	29 (42·6%)

() = Patients treated with steroids.

epithelium in diabetes in 1883. Kamocki (1887) later studied the subject in detail. According to Yanoff *et al.* (1970) this phenomenon is seen in 40% of enucleated eyes from diabetic patients in which the material within the vacuoles has been identified as glycogen. While diabetes mellitus provides the most frequent and most florid example of MIPE, other conditions show somewhat similar changes. The size of the vacuoles can be diagnostic. In diabetes they often attain a much larger size than in any other condition in which it occurs. The diabetic pigment layer may balloon 2 to 3 times the normal width. In the other conditions they are really microcysts that do not appreciably widen the pigment layer. The systemic mucopolysaccharidoses, particularly MPS I, II, and VI, have similar appearing but smaller microcysts that are filled with membrane bound vacuoles containing mucopolysaccharide (Seelenfreund *et al.*, 1968; Topping *et al.*, 1971; Kenyon, 1976). Unlike the changes in diabetes these cystic changes are also seen in the non-pigmented ciliary epithelium and other epithelial tissues in the eye. In 1968 Seelenfreund *et al.* reported MIPE in a case of Menkes's kinky hair disease, a condition in which serum copper is abnormally low. This finding was later confirmed by Wray *et al.* (1976). It has also been appreciated by ophthalmic pathologists that some neonatal eyes have MIPE. We noted such cysts in enucleated eyes from patients who were on high-dosage, long-term systemic corticosteroids.

The present study emphasises the fact that MIPE are a common pathological feature associated with many disorders, and in particular with a variety of neoplasms. They are also commonly found in patients who have been on high-dosage corticosteroids. Our study in no way reflects the incidence of the condition, for it was obtained from very selected material. The eyes from cancer patients were generally from those with widely disseminated disease and not from those with limited disease. Furthermore, some of the diagnoses may not be precise, for example, 'renal failure', 'pneumonia',

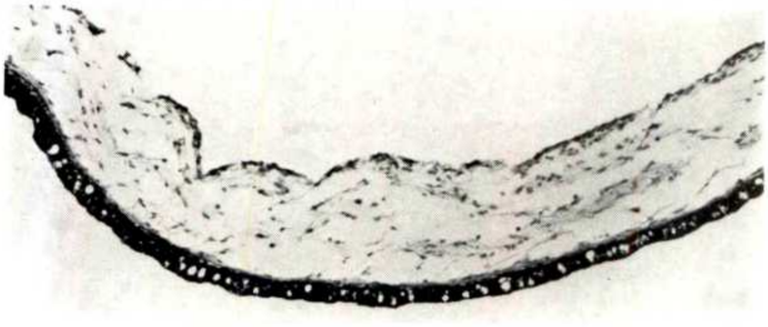

Fig. 1 *Microcysts in iris pigment epithelium found in association with alveolar cell carcinoma of lung (H and E; ×58)*

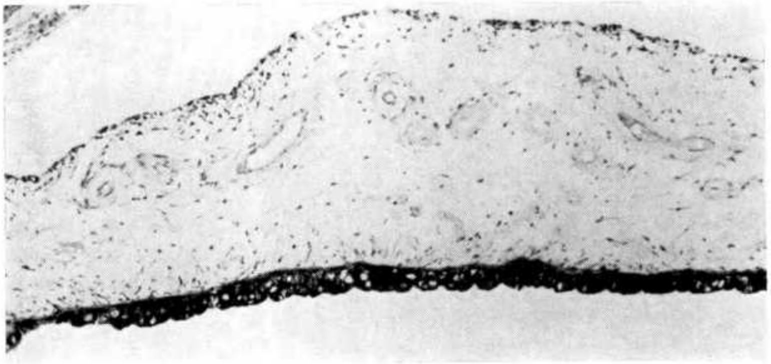

Fig. 2 *Microcysts in iris pigment epithelium found in association with prostatic adenocarcinoma (H and E; ×58)*

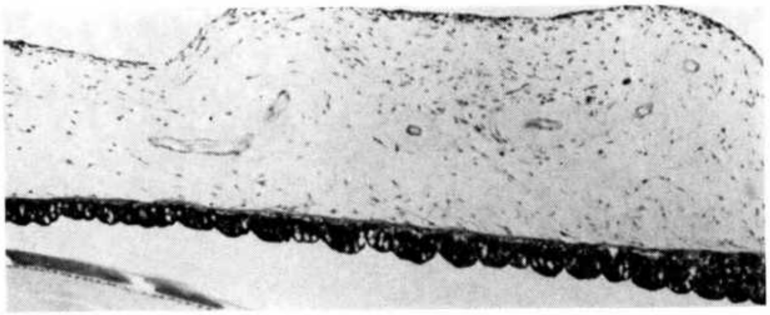

Fig. 3 *Microcysts in iris pigment epithelium found in association with acute lymphocytic leukaemia (H and E; ×58*

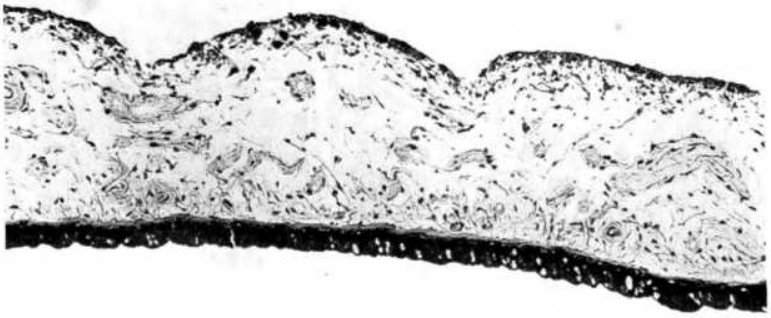

Fig. 4 *Microcysts visible in iris sectioned at 9 μm but not apparent at 15 μm* (Fig. 5) *(H and E; ×58)*

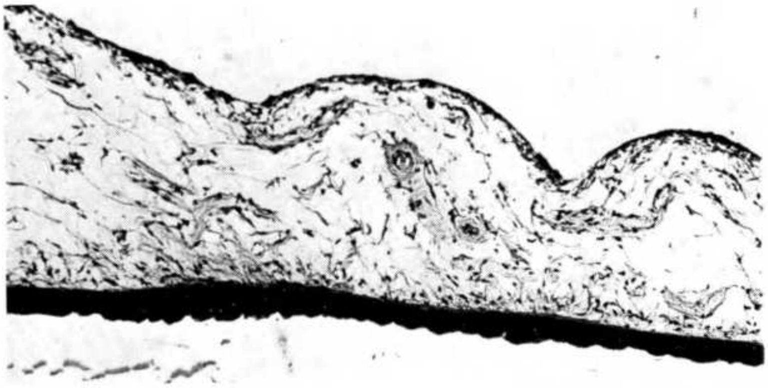

Fig. 5 *Microcysts visible in iris sectioned at 9 μm* (Fig. 4) *but not apparent when sectioned at 15 μm (H and E; ×58)*

etc. However, diabetes could be excluded in all cases.

One aspect of this study may explain why we have found such a high incidence of MIPE. Until 2 decades ago and in many laboratories until much more recently most eyes were processed in celloidin. This generally necessitated making relatively thick histological sections, usually 15 μm or more thick. We have shown that such thick sections will often mask the presence of any but the larger MIPE. The thinner the sections the more obvious are the microcysts.

We have not identified the material found in the MIPE in the cases described in our present study. Whether such cysts contain glycogen or another storage or breakdown product is not known. One can but speculate that neoplasms significantly alter the body's metabolism and lead to deposits in the iris pigment epithelium and also that exogenous steroids may have a similar role. Biochemical, histochemical, and ultrastructural studies will have to be performed to provide us with the answer.

We find fascinating the fact that so little is known about the function of the iris pigment epithelium. Long considered little more than a curtain to exclude light from the eye, perhaps the iris pigment epithelium will turn out to have multiple functions presently unknown to us.

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Cauterising iris scissors

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SUMMARY The cauterising iris scissors described here are a modification achieved by suitably insulating the standard De Wecker's iris scissors. This modification provides in addition to cutting an advantageous cauterising effect, which could prove useful in the surgery of eye conditions with high risk of bleeding or metastasis. It utilises the optimum electric current range of 20–40 mA.

A pair of standard DeWecker's iris scissors has been completely insulated, apart from the blades, with a dip coated PTCFE plastic, Insulast (GU Manufacturing Co. Ltd.). The blades, apart from the cutting edges and inner surfaces, have been insulated with a spray-on PVC plastic coating, Vycoat (Figs. 1 and 2). These scissors are electrically connected to the output of the Manchester Diathermy Unit through a lead which is fixed to their handle. The sharp edges of the blades act as an active electrode. They cut, coagulate the tissues, and seal the blood vessels as they cut.

With the intention of using the scissors as a cauterising and cutting instrument for surgery on the iris this study attempts to discover the safe range of the electric currents to be used that do not produce undesirable visible effects on the irides of enucleated ox eyes and irides of anaesthetised rabbits.

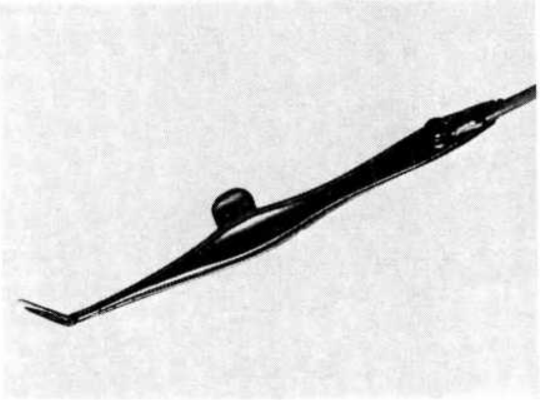

Fig. 1 *Cauterising iris scissors*

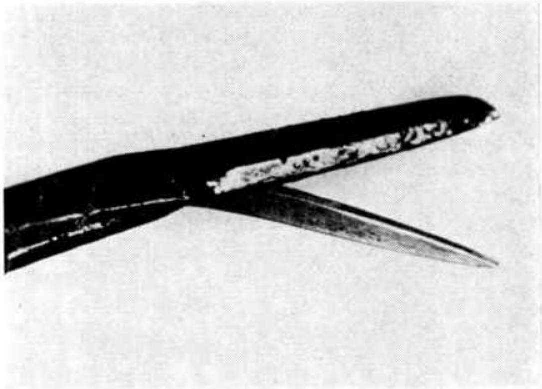

Fig. 2 *Cutting edges and inner surfaces have not been insulated*

Two of the rabbits' eyes on which these scissors were used to produce broad iridectomies were observed postoperatively for 1 week. Both eyes were then enucleated and one was submitted for histological examination.

Results

ENUCLEATED OX EYES

Current root mean square values	*Cutting action of scissors/visible effects on iris*
5 mA 20 mA 40 mA 45 mA 50 mA	Smooth cut, no fumes, and no sticking of iris tissue to the blades
65 mA	Some fumes, very little charring
75 mA	More fumes, not cutting smoothly, iris tissue becomes rubbery
95 mA	Fumes +, not cutting smoothly, iris tissue becomes rubbery
100 mA	Fumes and noise, charring +

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LIVE RABBITS' EYES

The rabbit eye, when enucleated, was placed in 10% formol saline for fixation over a 3-day period and was then paraffin processed. The eye was cut transversely through cautery marks at 5 μm and sections were stained by haematoxylin and eosin.

Current RMS values	*Cutting action of scissors/ visible effects on iris tissue (Figs. 3 and 4)*	*Histological findings ((Figs. 5, 6, and 7)*
Zero	Bleeding + or punctate bleeding from the cut edges; no white band near the margins	Haemorrhage, vasodilatation. Stromal infiltrations with inflammatory cells
10 mA	As above	Tissue damage due to crushing effect of scissors
20 mA	Smooth cut, no bleeding, white band (cauterising effect) visible	Mild vascular reaction. A few erythrocytes. Structureless tissue near the margins over a small area
30 mA	As above	
40 mA	No bleeding, smoother and cleaner radial cut, less force required to cut. White band near the cut margins and no radial shortening of the margins	A few erythrocytes present in the area, probably derived from the first 2 cuts. Inflammatory response absent
45 mA	White band. Cut margins became round with some radial shortening	This cut was not sufficiently visible in the sections, but shows no haemorrhage or infiltration response
50 mA	White band with obvious radial shortening	

The current range between 20–40 mA is significant for the following reasons. (1) There is no visible haemorrhage from the cut edges of the iris. (2) A white band, which is due to cauterising effect, appears at the margins of the cut iris at 20 mA. This white band gets wider with higher currents. (3) Inflammatory response is absent. (4) Histologically it is impossible to recognise the damage to the iris tissue along the cut margins corresponding to the cauterising band.

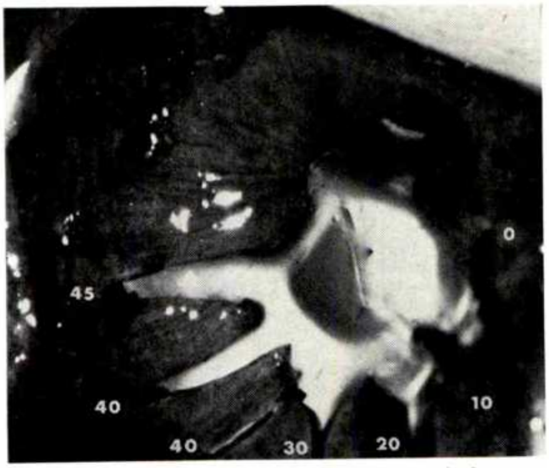

Fig. 3 *Radial cuts made on the rabbit iris with the cauterising iris scissors using different strengths of electric currents. From right to left: 0, 10, 20, 30, 40, 40, 45 mA*

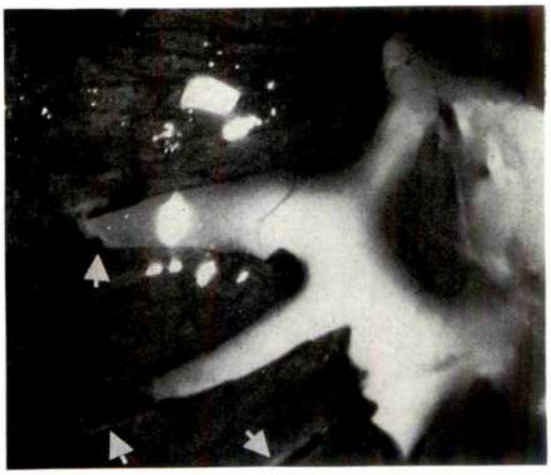

Fig. 4 *High power of the radial cuts, made with 40 and 45 mA currents. Cauterising band is clearly visible (arrowed)*

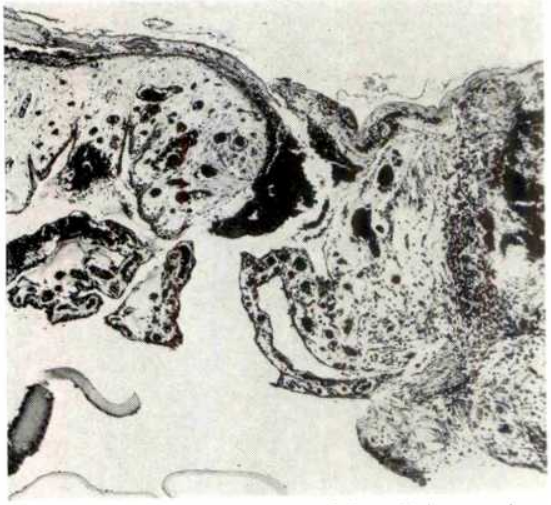

Fig. 5 *Histological appearance of the radial cut made with cauterising iris scissors without electric current*

RABBIT EYE ONE WEEK AFTER BROAD IRIDECTOMY

A current of 40 mA was used to perform a broad iridectomy under general anaesthesia (Fig. 8).

Cyclopentolate 1% drops and chloramphenicol drops were instilled in the rabbit's eye, each 3 times a day. A photograph of the eye 1 week after the operation shows an atrophic band along the cut margins which has replaced the cauterised band. (Fig. 9). Histological examination of this eye did not disclose any visible effect on the iris margins along the cut and adjacent tissues. There was no inflammatory response or fibrosis (Fig. 10).

Discussion

It would seem that the optimum current range that produces a clean-cut and adequate coagulation

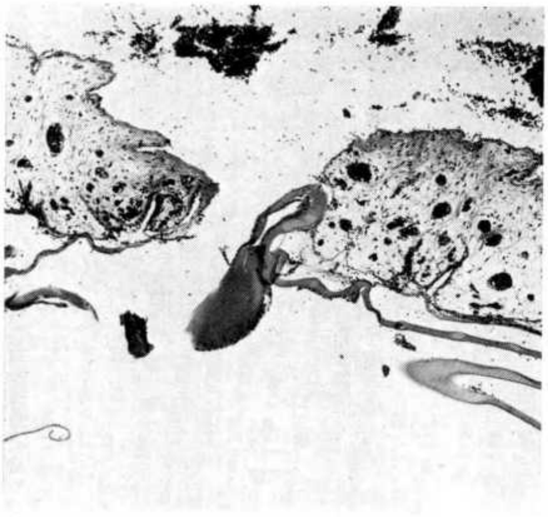

Fig. 6 *Radial cut with 20 mA current*

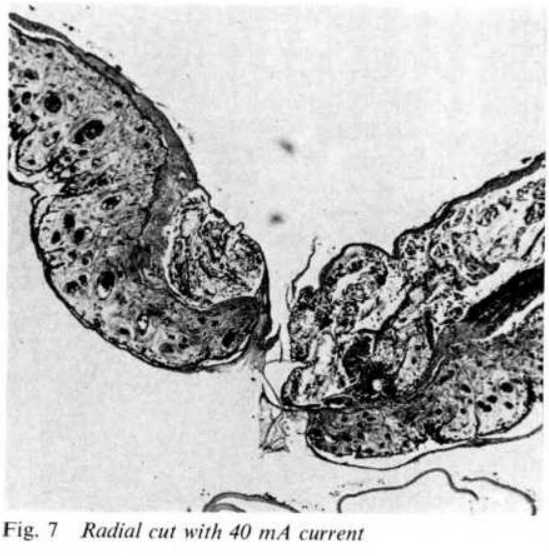

Fig. 7 *Radial cut with 40 mA current*

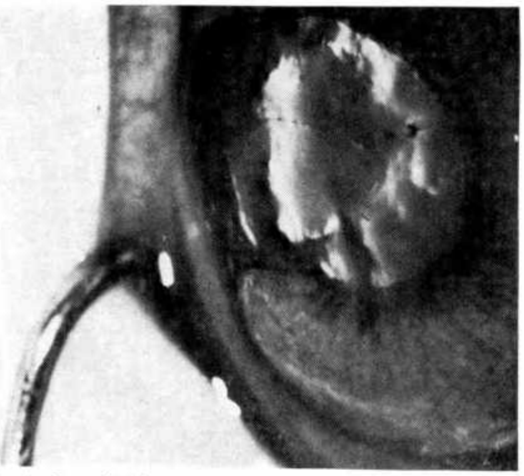

Fig. 8 *Broad iridectomy on rabbit eye using 40 mA current*

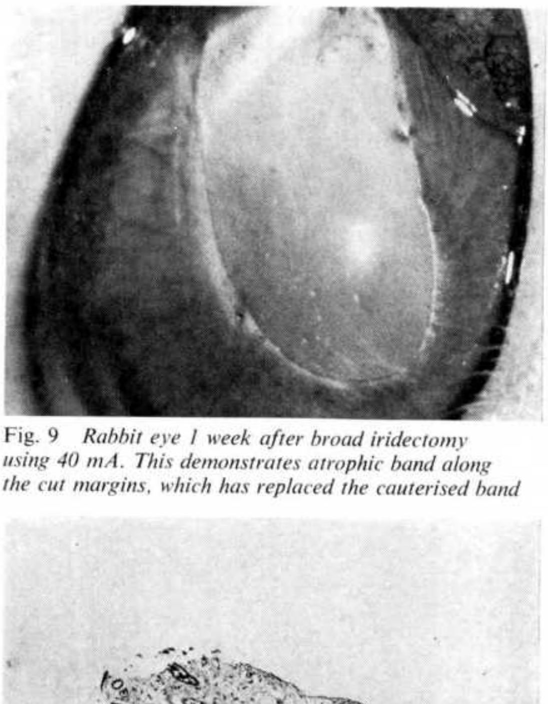

Fig. 9 *Rabbit eye 1 week after broad iridectomy using 40 mA. This demonstrates atrophic band along the cut margins, which has replaced the cauterised band*

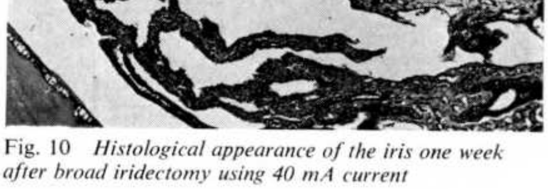

Fig. 10 *Histological appearance of the iris one week after broad iridectomy using 40 mA current*

without contraction of edges, fumes, or charring in the rabbit eye is 20–40 mA.

The DeWecker's Scissors have been further modified by soldering to the handle a socket to allow the diathermy lead to be detached and by coating the entire surface of the scissors, apart from the cutting edges and inside surfaces of the blades, with Insulast. In this way the modified scissors have been made suitable for autoclaving.

The use of this modification on DeWecker's scissors is proposed for the surgery of neovascular conditions of the iris, associated with glaucoma; neoplastic conditions of the iris, ciliary body, and anterior choroid which require excision; eyes with a high risk of bleeding in patients on anticoagulants.

We thank the Department of Medical Illustration at the University Hospital of Wales for the photographic work in this paper.

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Juxtapapillary choroiditis in association with rising antichlamydial antibody

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SUMMARY We present the case of a 21-year-old girl with a uniocular juxtapapillary choroiditis. During the course of her illness the titre of antichlamydial IgG increased from 1/32 to 1/4096 against *Chlamydia trachomatis* TRIC serotypes J and C, and antichlamydial IgM appeared in her blood. Toxoplasma dye test was positive at a level of 1/128 but no increase in the titre of antibody was detected during the course of her infection. The relevance of these findings to her ocular lesion is discussed.

Peripapillary choroiditis was first described by Griffiths (1897), who indicated that the condition could be difficult to differentiate from papillitis. A series of 38 cases of choroiditis (Friedenwald, 1902) contained 10 with inflammation adjacent to the optic disc, but for some reason the description has been associated with Edmund-Jensen (1908) who published 4 cases.

Juxtapapillary choroiditis appears to differ only in its geographical location from other recognised forms of choroiditis. Toxoplasmosis has been reported as the most frequent cause of the disease on the grounds of rising titre of antitoxoplasma antibody in the blood (Duke-Elder, 1966). However, tuberculosis and streptococcal infections are also considered to be responsible for certain cases of choroidits.

We report here a case of juxtapapillary choroiditis in which the patient had serological evidence of an active chlamydial infection and discuss the relationship of this to her ocular condition.

Case report

A 21-year-old black woman (born in France) presented with a history that 5 days previously she had noticed a transient redness and watering of the right eye. After this there was pain on eye movement, increasing blurring of vision, and superior field loss. Her left eye was amblyopic, she had been born prematurely at 6½ months and had received oxygen in an incubator for several weeks. Otherwise there were no significant features in her previous general health or ocular history. She was sexually active and had had an illegitimate baby 6 months previously.

On clinical examination her acuities were 6/18 correcting to 6/9 in the right eye with a –3D lens and 1/60 in the left with a –16D lens. Examination of palpebral and bulbar conjunctivae and both anterior segments were normal; there were a few cells in the right vitreous, though the left was clear. The right optic disc was swollen with a white retinal and subretinal infiltration inferiorly (Fig. 1), and the disc and adjacent vessels leaked fluorescein (Fig. 2). Otherwise the fundus was normal. The left optic disc was highly myopic with traction of the vessels to an area of pigmentation and scarring along the temporal area consistent with a mild degree of retrolental fibroplasia in this eye.

She was admitted to hospital for thorough investigation in view of the fact that this was her only functional eye. General examination was normal. Skull and chest *x*-rays were normal. Haematology showed Hb 14·1 g/dl, leucocytes 10·3 $\times 10^9$/l (neutrophils 67%), erythrocyte sedimentation rate (ESR) 3 mm/h, fibrinogen 3·19 g/l, with a normal blood film and negative Paul-Bunnell test. Tests of renal and hepatic function were normal, as was the serum calcium. Cultures of the blood and urine grew no pathogens. Total protein was 62 g/l (albumin 41 g/l), IgG 11·7 g/l, IgA 1·55 g/l, IgM 1·55 g/l, and C_3 1·15 g/l. Autoantibodies were present to smooth muscle and mitochondria. The latex agglutination test was negative. No parasites were found in the faeces. The cerebrospinal fluid was normal, and serological tests for syphilis,

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including *Treponema pallidum* haemagglutination test, Venereal Disease Reference Laboratory flocculation test, and absorbed fluorescent treponemal antibody test were all negative.

She received a course of ACTH (80 units/day) for 5 days, which was then stopped. After this her leucocyte count rose to $14\cdot7\times10^9/l$ (56% netrophils) and was $12\cdot7\times10^9/l$ 5 days after this. She complained of increasing visual loss about 2 weeks after admission, and prednisolone 60 mg/day was recommenced. The white blood cell count rose to $23\cdot8\times10^9/l$ (79% neutrophils) and slowly decreased to normal levels over the next 4 weeks.

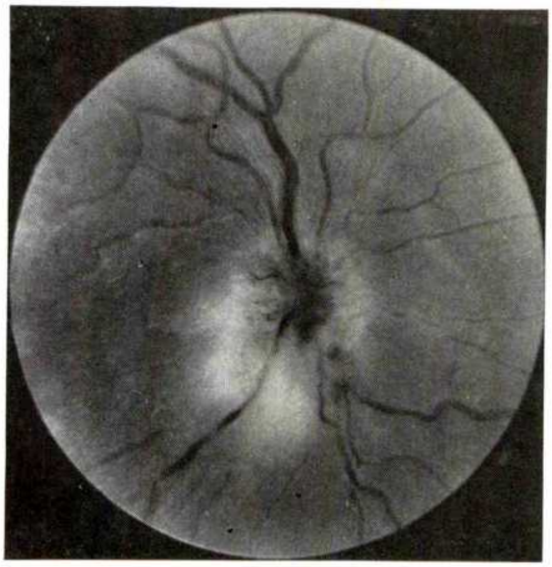
Fig. 1 *Right optic disc showing retinal and subretinal exudation inferiorly*

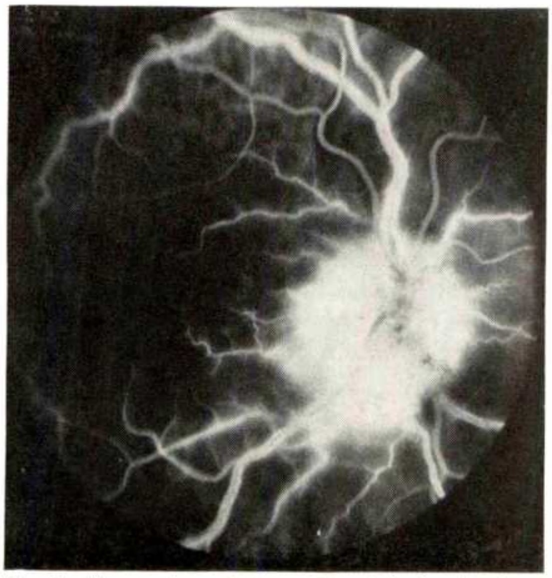
Fig. 2 *Fluorescein angiogram of the right disc showing leakage of fluorescein from disc and vessels in the late stage*

No significant rise in antibody titre was found against herpes simplex, herpes zoster, cytomegalovirus, measles, mumps, adenovirus, influenza A+B, parainfluenza, respiratory syncytial virus, and hepatitis B. Antibody titres against mycoplasma, *Rickettsia burnetti, Salmonella typhi,* and *Salm. paratyphi* were not significant, and tests for toxocara were negative. A Mantoux test to 1:10 000 PPD was negative. The toxoplasma dye test on a blood sample collected 2 weeks from the onset of infection showed titres of 1/128; no IgM antibody was present and a further specimen 2 weeks later did not show a rise in titre. The Kveim test was negative. Shortly after leaving hospital the patient failed to attend for follow-up.

Chlamydial serology by the modified micro-IF test (Treharne *et al.*, 1977a) showed a significant rise in the titre of antichlamydial IgG from 1/32 to 1/4096 during the course of the disease and the presence of antichlamydial IgM at a titre of 1/16 (Table 1). The highest IgG titre was against *Chlamydia trachomatis* TRIC serotypes J and C.

Clinical examinations of the genital tract and abdomen showed no abnormality in the cervix,

Table 1 *Detection of immunoglobulin class of antichlamydial antibody in the blood by a micro-IF test*

Chlamydiae	*18 Dec. 1977 12 days from the onset*		*12 Jan. 1978 5 weeks from the onset*		*2 Feb. 1978 8 weeks from the onset*	
C. trachomatis	*IgG*	*IgM*	*IgG*	*IgM*	*IgG*	*IgM*
A	32	0	256	16	32	0
B	32	0	256	16	32	0
C	32	0	*4096*	16	*2048*	0
D	0	0	2048	16	1024	0
E	0	0	2048	16	1024	0
F	0	0	2048	16	1024	0
G	0	0	2048	16	1024	0
H	0	0	2048	16	1024	0
I	0	0	2048	16	1024	0
J	32	0	*4096*	16	*2048*	0
K	0	0	2048	16	1024	0
LGV I	0	0	128	16	64	0
II	0	0	128	16	64	0
III	0	0	128	16	64	0
C. psittaci	0	0	128	16	32	0

urethra, rectum, or the Fallopian tubes. No chlamydiae were isolated from the cervix, and the micro-IF test on cervical secretion was negative for antichlamydial antibody. Culture of a blood sample collected 2 weeks after the onset of papillitis was sterile after 15 days' incubation. Urine culture produced no significant growth of bacteria.

Discussion

The development of blurred vision associated with pain in this patient, together with the absence of any previous chorioretinal scarring, suggested that her juxtapapillary lesion had been recently acquired and that it might be due to an active infection because of the increasing white blood cell count.

Serological evidence for infection by a wide variety of organisms was sought. Of these, the tests for chlamydiae and toxoplasma were positive. The micro-IF tests on a sample of blood collected 2 weeks after the onset of papillitis showed antichlamydial IgG at a level of 1/32 against *C. trachomatis* TRIC serotypes A, B, C, and J. TRIC serotypes A, B, and C are generally associated with hyperendemic trachoma of eye-to-eye transmission, which is common in Asia and Africa, and TRIC serotype J is associated with chlamydial genital infection common in developed countries. The presence of IgG at a low level of 1/32 against these agents suggests that this patient may have been exposed to chlamydiae in the past or is at present suffering from a chlamydial infection.

The second sample of blood collected 3 weeks later (5 weeks after the onset of choroiditis) showed a rise in IgG titre to the very high value of 1/4096 against *C. trachomatis* TRIC serotypes J and C, and antichlamydial IgM at a titre of 1/16. The significant rise in the titre of antichlamydial IgG and the presence of IgM during the course of the disease strongly suggests that our patient had an active chlamydial infection, probably due to TRIC serotypes J or C.

TRIC serotype J is a member of the group which is associated with chlamydial genital infection in men and women, including non-specific urethritis in men, non-specific genital infection in women, pelvic inflammatory disease in women, and ocular TRIC infection of sexually transmitted origin (Treharne *et al.*, 1977a, b) common in the developed countries of the Western world. Studies by Wang and Grayston (1975) and Treharne *et al.* (1977a) have shown that there is a strong serological cross-reaction between TRIC serotype C of hyperendemic trachoma and TRIC serotype J of ocular-genital infections. However, from the epidemiological viewpoint it is likely that in our patient TRIC serotype J may have been responsible for the infection rather than TRIC serotype C. The low level of IgG against LGV agents and *C. psittaci* detected in the blood of our patient may exclude these organisms as the cause of infection.

The very high titre of antichlamydial IgG obtained in this case is much higher than the average titre of antibody normally detected in patients with chlamydial urethritis or cervicitis (Treharne *et al.*, 1977b), but it is within the range of the titres which have been obtained in patients with pelvic inflammatory disease (Treharne *et al.*, 1979). In this patient clinical and laboratory investigations of the genital tract and abdomen revealed no evidence of chlamydial infection of the cervix or Fallopian tubes. However, these negative results cannot rule out the possibility of an occult urogenital chlamydial infection or a latent chlamydial pelvic infection, which might be responsible for the intraocular infection.

The role of chlamydiae in the production of human disease is being increasingly recognised. Recent studies have shown that *C. trachomatis* may cause systemic infection, that is, pneumonitis in newborn babies (Beem and Saxon, 1977), pelvic inflammatory disease (Mardh *et al.*, 1977; Treharne *et al.*, 1979), peritonitis, and perihepatitis in sexually active women (Muller-Shoop *et al.*, 1978). *C. trachomatis* has been isolated from the cervix of 5 to 12% of women attending for routine prenatal examination with no obvious cervical inflammatory changes (Alexander *et al.*, 1977) and in up to 31% of women attending sexually transmitted diseases clinic (Hilton *et al.*, 1974).

The toxoplasma dye test was positive at a level of 1/128 in the blood taken at 2 weeks after the onset of symptoms and 2 weeks later when the patient's choroiditis was well established. No IgM antibodies were found on either occasion, though the relevance of this to ocular infections is not known. These results must be interpreted with caution. Positive titres of 1/16 or greater are found in up to 40% of the adult population and titres of 1/256 in 1% of healthy adults (Public Health Laboratory Statistics, 1969).

It would be most unlikely that our patient had a recently acquired toxoplasmosis. This is a rare infection, and ocular involvement in the absence of systemic symptoms or signs is exceptionally rare. Furthermore, the dye test titres detected in this patient are too low to indicate such an active infection (Perkins, 1973). However, it is more difficult to exclude congenital toxoplasmosis as the cause of her ocular lesion. In some studies (Perkins, 1961) up to 96% of focal posterior choroiditis is attributed to this agent. In order to be certain of this diagnosis signs of previous chorioretinal scarring, intracranial calcification, and a rise in dye test titre should be demonstrated. However, occasionally histological evidence of ocular toxoplasmosis has been found in the presence of a negative dye test (Franceschetti and Englebrecht, 1964), and a fresh focal choroiditis with no evidence of previous scarring has been found with intracranial calcification on skull *x*-ray and a positive dye test (Perkins, 1973).

The result of our investigation suggests that the cause of our patient's disease is likely to be chlamydiae rather than toxoplasma. However, further investigations will be necessary to define whether or not chlamydial organisms do have a role in this disease.

We thank Mr R. Sennhenn for taking the photographs.

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Double-blind clinical trial of topical steroids in anterior uveitis

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SUMMARY We present the results of a double-blind trial comparing the efficacy of betamethasone phosphate 0·1%, clobetasone butyrate 0·1%, and placebo in the treatment of acute unilateral nongranulomatous uveitis. The 2 steroids were equally comparable in improvement of the patients' symptoms, though betamethasone phosphate was significantly more effective than clobetasone butyrate in improving the ocular signs of uveitis. However, clobetasone butyrate had significantly less effect on raising intraocular pressure in known steroid responders and ocular hypertensives than did dexamethasone. The use of a bolometer as an objective measure in uveitis was significant only in the more severe cases of uveitis. In comparing the placebo group of patients with those on topical steroids, the former group, though improving, appeared to lag behind by approximately one week. Four cases on placebo, however, had to be withdrawn because of worsening of the condition. Mild cases of anterior uveitis would probably resolve without using topical steroids.

Although uveitis is essentially a self-limiting disease, it is none the less necessary to institute prompt treatment to reduce the inflammatory response, relieve pain, prevent posterior or peripheral anterior synechiae, and lower intraocular pressure in those eyes with secondary glaucoma.

Before the introduction of steroids mydriatrics were the mainstay of therapy, acting by abolishing the dilatation and constriction of the pupil and pull of the ciliary body during the movement of accommodation, thereby reducing iris and ciliary spasm and hence relieving pain and, in addition, breaking down the posterior synechiae. Steroids have been used locally as the standard form of therapy in acute and chronic uveitis since the early 1950s, their mechanism of action being to reduce the exudative inflammatory process. This is achieved to some extent by inhibiting capillary permeability, thereby decreasing the cellular and protein leakage from the circulating blood into the aqueous during inflammation. However, there have been no double-blind studies to evaluate therapy in this field.

Topical corticosteroid therapy can cause side effects and involves such hazards as potentiation of herpes simplex and other viral diseases (Patterson and Jones, 1967), increased susceptibility to fungal infections (Ley and Saunders, 1956), and possible increased spread of bacterial infection (Mitsui and Hanabusa, 1955). A specific ocular complication of local steroid therapy may be the increase in intraocular pressure that occurs in genetically predisposed individuals (Goldman, 1962; Becker and Mills, 1963; Becker, 1965) and in fact topical steroids are being used as a provocative test (Becker and Ballin, 1965).

It would seem reasonable to question the efficacy of steroids in uveitis, and this controlled double-blind clinical trial has therefore been devised to assess the response of anterior uveitis to topical steroids.

Patients and methods

This was a double-blind trial between-patient study involving 3 treatment regimens: betamethasone phosphate (0·1%), clobetasone butyrate (0·1%), and placebo eyedrops. Patients selected for study were those presenting to the Casualty Department of St. Paul's Eye Hospital, Liverpool. Sixty patients were entered in the trial, all being cases of acute unilateral nongranulomatous anterior uveitis. Twelve did not complete for reasons stated below, and are omitted from Table 1.

On admission of the patient to the trial a clinical history was taken and a record form was completed. Details of the patient's subjective assessment of the discomfort of the eyes, a full detailed slit-lamp

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Table 1 *Summary of patient details*

Treatment	*Clobetasone butyrate*	*Betamethasone phosphate*	*Placebo*
Number in group	16	18	14
Number of males	13	13	9
Number of females	3	5	5
Average age (years)	47	55	48
Range of age (years)	27–70	36–74	46–70
Affected eye: right	7	7	9
left	9	11	5
Recurrent iritis	11	13	8
Range of years since first episode of iritis	½–21	1–25	1/3–17
Number of days of symptoms before treatment:			
average	4	6	7
range	1–14	1–21	1–21

examination, visual acuity, and intraocular pressure were recorded on the patient record form. In addition corneal temperatures of both eyes were recorded with a bolometer (Mapstone, 1968a, b, c).

Patients were randomly allocated to clobetasone butyrate, or betamethasone phosphate, or placebo eyedrops. Comparative details for each group are given in Table 1. They were asked to instil the drops daily into the relevant eye using 2 drops 2-hourly each day for a period of 3 weeks. In addition, guttae atropinae 1% were instilled twice daily and, when necessary, acetazolamide for secondary glaucoma.

Patients were seen at 3, 7, 14, and 21 days for reassessment and recording of findings. In those cases in which the uveitis became worse they were reviewed daily. The scoring of symptoms and signs were as in Table 2.

Results

Symptoms and signs were analysed separately. Initially, the Kruskal-Wallis one-way analysis of variance was used to determine if the 3 groups of patients were statistically different. If this test showed a difference, the Mann-Whitney U test was used to compare the individual pairs of treatment groups. In both tests the level of significance was taken as $P < 0{\cdot}05$. When correlating the signs and symptoms with eye temperature, the Spearman rank correlation coefficient (r_s) was calculated.

SYMPTOMS

There was no difference in the 3 groups initially, and betamethasone phosphate and clobetasone butyrate drops were significantly better than placebo after 3 days' treatment. There was a difference at 7 days, though this just failed to reach a statistical significance, probably owing to the small numbers of the placebo group. The difference between steroid and placebo groups did not reach a statistical difference after 14 days and 21 days (Fig. 1).

SIGNS

The 3 treatment groups were not significantly different initially. Although there was a difference between steroid and placebo treatments at 3, 7, and 14 days, it failed to reach statistical significance. However, the groups were different after 21 days of treatment, and betamethasone phosphate

Table 2 *Scoring of symptoms and signs*

Symptoms				
Blurring	Scored as:	0=absent		
Redness		1=mild		
Watering		2=moderate		
Photophobia		3=severe		
Pain				
Signs				
Ciliary injection	0=nil	1=moderate	2=marked	
Corneal oedema	0=nil	1=moderate	2=marked	
Keratic precipitate	0=absent	1=present		
Flare	0=nil	1=+	2=++	3=+++
Cells in aqueous	0=nil	1=+	2=++	3=+++
Cells in vitreous	0=nil	2=+	3=++	4=+++
Exudate	0=absent	3=present		
Posterior synechiae	0=absent	1=present		
Ptosis	mm difference between 2 eyes 0=absent	3=present		
Hypopyon	0=absent	3=present		

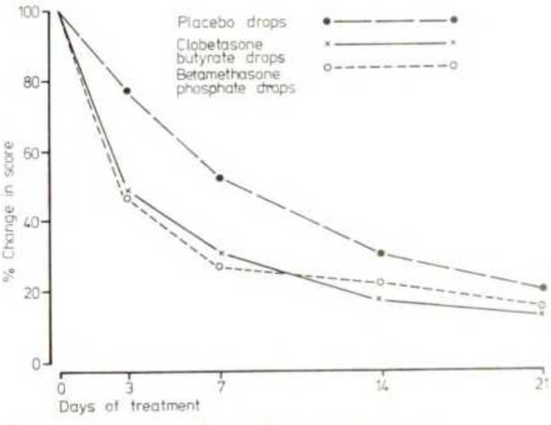

Fig. 1 *Percentage change in symptom scores*

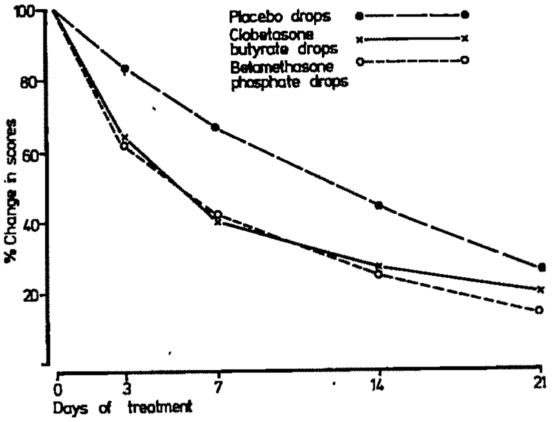

Fig. 2 *Percentage change in sign scores*

was significantly better than placebo; clobetasone butyrate was not significantly better than placebo (Fig. 2).

The correlation of initial eye temperature with initial symptom scores was $r_s=0{\cdot}33$; $t=2{\cdot}32$; $P<0{\cdot}05$.

The correlation of initial eye temperature with initial sign scores was $r_s=0{\cdot}24$; $t=0{\cdot}17$; $P>0{\cdot}05$.

Eye temperature was then correlated with selected signs: hypopyon, ptosis, exudate, cells in anterior vitreous, and ciliary injection; $r_s=0{\cdot}41$; $t=3{\cdot}46$; $P<0{\cdot}05$.

EVALUATION OF INTRAOCULAR PRESSURE CHANGES

The intraocular pressure changes in 5 cases (2 steroid responders and 3 ocular hypertensives) known to sustain raised intraocular pressures with topical steroids are shown for dexamethasone 0·1% t.i.d. for 6 weeks (Table 3) and in the same cases for clobetasone butyrate 0·1% t.i.d. for 6 weeks (Table 4). In case 1 clobetasone butyrate was stopped after 2 weeks as there was a significant pressure rise.

A summary of the results showing mean percentage of change in symptoms and sign scores with treatment is shown in Table 5. A formal analysis

Table 3 *After dexamethasone 0·1% 3 times daily for 6 weeks*

Case no.		*Baseline IOP mmHg*	*'C' tonography values µl/min/mmHg*	*Final IOP mmHg*	*'C' tonography values µl/min/mmHg*
1	Steroid responder	16	0·27	34	0·09
2	Steroid responder	17	0·23	32	0·16
3	Ocular hypertensive	20	0·15	29	0·14
4	Ocular hypertensive	28	0·09	37	0·05
5	Ocular hypertensive	24	0·06	36	0·07

Table 4 *After clobetasone butyrate 0·1% 3 times daily for 6 weeks. Treatment of case 1 was stopped after 2 weeks as there was a significant pressure rise*

Case no.	*Baseline IOP mmHg*	*'C' tonography values µl/min/mmHg*	*Final IOP mmHg*	*'C' tonography values µl/min/mmHg*
1	14	0·13	20	0·15
2	16	0·24	20	0·25
3	22	0·22	18	0·19
4	23	0·14	22	0·11
5	20	0·11	21	0·14

Table 5 *Summary of results*

	Days of treatment	*Clobetasone butyrate*	*Betamethasone phosphate*	*Placebo*
Mean % change in symptom scores on days of treatment	3	51·7	53·2	22·7
	7	69·0	73·4	47·4
	14	82·8	76·6	70·1
	21	86·2	84·7	79·4
Mean % change in sign scores on days of treatment	3	36·8	38·7	18·3
	7	59·4	58·6	33·9
	14	73·7	75·2	59·6
	21	80·5	86·2	74·3
Mean % change in sign and symptoms scores on days of treatment	3	42·7	45·5	20·4
	7	63·2	65·4	40·3
	14	77·3	75·8	63·6
	21	82·7	85·6	76·7
Number of patients where scores (signs and symptoms) rose greater than pretreatment level after treatment	—	1	1	6
Number of patients where scores (signs and symptoms) rose during treatment but not greater than pretreatment level		3	1	2

based on the clinical signs divided the 3 groups into mild and severe cases (Table 6). Those cases with flare, cells, and keratic precipitates only were classed as mild uveitis, while the severe cases on initial examination had, in addition, one or more of either ptosis, exudate, or hypopyon.

Figs. 3 and 4 show the duration of uveitis in mild and severe cases in each of the 3 treatment groups.

Twelve patients did not complete the trial. Four patients were withdrawn because of worsening of the condition and they were later found to have been on placebo eyedrops. One patient was given another medication in error after starting the trial, 1 patient was withdrawn after 7 days due to development of bilateral anterior uveitis, and 6 patients defaulted.

Table 6 *Formal analysis*

	Number of cases		
	Mild	*Severe*	*Total*
Clobetasone butyrate	9	7	16
Betamethasone phosphate	10	8	18
Placebo	9	9 (4 withdrawn)	18

Discussion

Steroids are used locally as the standard form of therapy in acute and chronic uveitis. Their efficacy is accepted (Duke-Elder, 1951; Duke-Elder *et al.*, 1951; Woods, 1951; Fitzgerald, 1951; Woods, 1952a, b; Ashworth, 1954), though there have been no controlled double-blind studies to evaluate therapy in this field.

A double-blind trial was devised with the following aims: (1) to determine the place of steroids in the treatment of acute anterior uveitis by comparing steroid and placebo treated groups of patients; (2) to determine the clinical efficacy of the steroid clobetasone butyrate compared with betamethasone phosphate; (3) to confirm that the measurement of corneal temperature is a useful objective parameter for the assessment of inflammation due to anterior uveitis and to establish the correlation between this and the subjective assessment by means of a scoring system for signs and symptoms (Ashford and

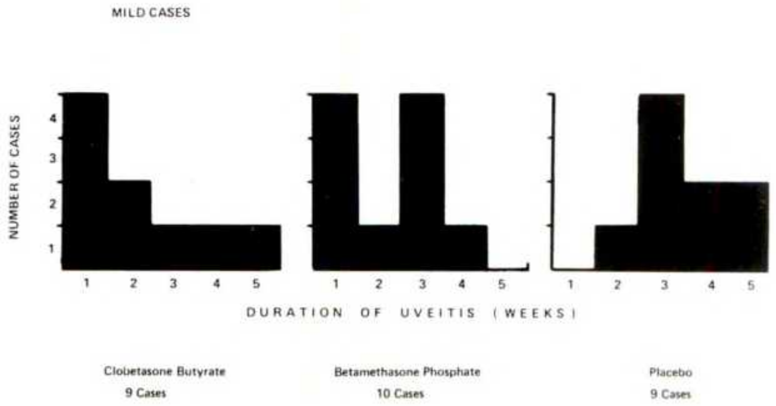

Fig. 3 *Histograms showing duration of uveitis in weeks in mild uveitis cases in each of the 3 treatment groups: clobetasone butyrate, betamethasone phosphate, and placebo*

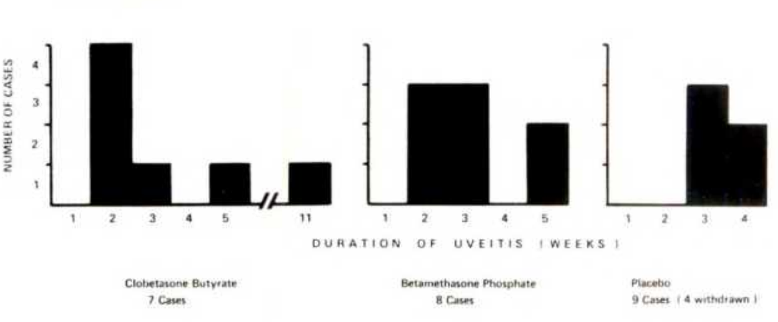

Fig. 4 *Histograms showing duration of uveitis in severe uveitis cases in each of the 3 treatment groups: clobetasone butyrate, betamethasone phosphate, and placebo*

Lamble, 1974); and (4) to evaluate intraocular pressure changes on clobetasone butyrate.

The results have shown, as regards symptoms, that although the steroid-treated group of patients were significantly better than the placebo-treated group within the first 10 days, there was no significant difference in the 2 groups between 14 and 21 days. There is therefore more improvement symptomatically in the initial stage of treatment in those patients on steroids than those on placebo. Of the improvement in signs, however, the patients on betamethasone phosphate were significantly better than the placebo group after 21 days. Clobetasone butyrate did not appear to be significantly better than placebo.

Figs. 1 and 2 show that the improvement of those patients on placebo lagged behind that of those on topical steroids by approximately 1 week. Therefore it could be argued that topical steroids are merely speeding up the resolution of an otherwise self-limiting disease by a period of 7 to 10 days.

One of the difficulties in evaluating steroids in the treatment of uveitis is that one is dependent on the subjective assessment of the signs and symptoms resulting from the inflammatory response. However, Mapstone (1968a, b, c) and Ashford and Lamble (1974) have shown that the assessment of corneal temperature by means of bolometry provides an objective parameter which is directly influenced by the degree of inflammation of the iris.

In the present trial series, however, the measurement of corneal temperatures became significant only in the severe cases with selected signs, such as hypopyon, ptosis, exudate, or cells in the anterior vitreous. The milder cases of uveitis did not show significantly different corneal temperatures when compared with the fellow normal eye.

As mentioned previously, however, 4 cases removed from the trial because of worsening of the condition were found to be on placebo. Three of the 4 cases had presented initially with severe uveitis—that is, ptosis or exudate, on the first visit—and the fourth case had presented with moderate uveitis initially with flare and cells, but developed ptosis and exudate at 14 days. As shown in Figs. 3 and 4, of the other 5 severe cases on placebo 3 had resolved by 21 days and the other 2 by 35 days. Two of these cases had exudate on the first visit only, 3 had ptosis and exudate initially, but one or other of these signs was abating after 7 days on the trial. Of the mild cases on placebo, 7 out of 9 were fully resolved by 28 days; the remaining 2 cases were fully resolved by 35 days.

The ability of topically applied corticosteroids to cause ocular hypertension in susceptible individuals is one of the factors limiting their usefulness. Clobetasone butyrate was evaluated to see if it had a reduced propensity to cause a rise of intraocular pressure when compared with dexamethasone. The results have shown that there was no increase in intraocular pressure in 4 out of 5 cases on clobetasone butyrate, the remaining case being withdrawn after 2 weeks because of a pressure rise. Whereas all 5 cases on dexamethasone responded with a pressure rise, it appears that clobetasone butyrate shows a dissociation of anti-inflammatory from ocular hypertensive effects.

From this trial series it would appear that milder cases of uveitis, without inflammatory ptosis or exudate, resolve without topical steroids and that only those cases in which these signs exist need have topical steroid therapy. Certainly the more severe cases of anterior uveitis have inflammatory ptosis, exudate, and even hypopyon, which was why these signs were given high loading scores in the scoring system. Do all cases of anterior uveitis necessarily require topical steroids? Further trials are probably needed on a larger series of patients before this question can be satisfactorily answered.

Our thanks are due to Mr Mapstone for his helpful guidance and assistance throughout the trial and in the presentation of this paper. We also thank Dr Stuart R. Walker and Mrs Louise Eilon of Glaxo Research Ltd. for their considerable assistance with this project, including statistical analysis and providing material for the study, and Miss Carol Jones for secretarial assistance.

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Lysophosphatidyl choline in the aqueous humour during ocular inflammation*

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SUMMARY Phospholipase A and lysophosphatidyl choline (LPC) have been shown to induce significant changes in the lens permeability in vitro to cations and soluble proteins. During uveal inflammation, in various experimental models and in man as well, the levels of LPC in the aqueous humour have been shown to reach values which are harmful to the lens in vitro. In addition, a phospholipase is thought to be activated during the antigen + antibody + complement sequence. The possible significance of these findings is discussed in relation to the pathogenesis of complicated cataracts in uveitis and the possible role of the lens as a source of autoantigens in recurrent uveitis.

Phospholipids are an essential constituent of every cell membrane. According to a recent theory the 'framework' of cell membranes is formed by a bilayer of lipids whose hydrophilic 'heads' form the internal and external surfaces, while hydrophobic 'tails' join in the centre of the membrane. In intracellular membranes lipids consist mainly of phospholipids, while cytoplasmic membranes contain phospholipids, glycolipids, and neutral lipids (Capaldi, 1974).

Phosphatidyl choline (lecithin) is essential among membrane phospholipids and is hydrolysed by ubiquitous enzymes, phospholipases, to lysophosphatidyl choline (lysolecithin or LPC). Changes in LPC levels in a given tissue and/or fluid may thus be considered as an index of changed phospholipase activity. In the anterior chamber of the eye, however, an increase in the LPC level may be due also to the breakdown of a blood-aqueous barrier (Cotlier *et al.*, 1976) specific for phospholipids.

Normal rabbit aqueous contains 2·3 (±1·5) μgLPC/ml according to Varma and Reddy (1972), 4·3 μg according to Cotlier (1976), 1·46 (±0·78) μg in our experiments.

Local increases of phospholipase A and LPC (the former through a likely direct action on membrane phospholipids and the latter acting on the same substrate as a 'detergent') may induce changes in the normal lens permeability. Cotlier *et al.* (1975) have shown in vitro that 7·5 μgLPC/ml were enough to cause a significant gain of Na^+ and water to a lens in culture. We have shown that 10 μgLPC/ml induce a more important derangement in the lens permeability, allowing soluble lens proteins to leak out in the incubation medium (Secchi *et al.*, 1976b; D'Ermo and Secchi, 1977). Similar results have been obtained in the presence of 0·33 μg/ml of phospholipase A. The leakage of cytoplasmic constituents under these situations is probably due to membrane ruptures following cellular swelling.

Any situation in which phospholipase A and/or LPC levels in the aqueous reach or exceed the threshold shown harmful to the lens is therefore a potential cause of cataract. In addition, the leakage of soluble lens protein, immunogenic as 'sequestered antigens', may lead to intraocular inflammation, possibly recurrent, by an autoimmune mechanism.

We thought it interesting to study LPC levels in the aqueous during experimental allergic and clinical uveitis. An increase beyond the levels known to be harmful might be relevant to the pathogenesis of complicated cataracts in uveitis and to the possible role of the lens as a source of autoantigen in the self-perpetuation of recurrent anterior non-granulomatous uveitis.

Materials and methods

Experimental allergic uveitis was induced by Eifrig and Prendergast's technique, modified by D'Ermo *et al.* (1975). Intravenous injections of an antigen

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into a rabbit whose anterior chamber was grafted with a piece of autologous lymph node 'activated' against the same antigen were followed by anterior uveal inflammations. The lipids were extracted according to the technique described by Bligh and Dyer (Sheltawy and Dawson, 1969). The residues, obtained by removing the solvent under nitrogen, were dissolved in a chloroform-methanol mixture (1:1 v/v) and the lipids separated by thin-layer chromatography with the use of a chloroform-methanol-acetic-acid-water solution in the ratio 25:15:4:2.

Phospholipids spots were visualised on precoated silica gel plates (Precoated TLC Plates Silica Gel 60 F-254, Merck, Darmstadt, BRD) by exposure to iodine vapour and identified by standards run simultaneously. The gel from the areas containing the LPC was scraped off the plate and transferred to suitable tubes. Gel from adjacent areas of approximately the same size but containing no lipids was also scraped off and used as blank in the assay. Phospholipid phosphorus was estimated at ultramicrolevel as described by Bartlett (1959).

Results and discussion

The results of our experiments in vitro, which confirm and extend Cotlier's investigations, showed that 7·5 to 10 µgLPC/ml represents the minimum level clearly harmful to the lens (Secchi *et al.*, 1976b). LPC at this level is responsible for a derangement of the normal lens permeability to cations and, later, to its own soluble proteins.

Samples of aqueous humour drawn in the course of experimental allergic uveitis showed levels of LPC much higher than in normal aqueous, very close to those shown to be harmful in vitro (Table 1).

Aqueous taps performed in patients suffering from anterior non-granulomatous uveitis showed similar results: in these cases LPC levels were also significantly increased, with a clear correlation between rate of increase and severity of inflammation.

Table 1 *Levels of LPC in samples of aqueous humour*

In normal aqueous (rabbit)	1·46 ± 0·78 µg/ml
Harmful in vitro to normal rabbit lens:	
(a) gain in Na$^+$ and water	7·5 µg/ml*
(b) Leakage of soluble proteins	10·0 µg/ml†
In uveitic aqueous:	
(a) Rabbit	9·35 ± 2·7 µg/ml
(b) Man	
(1) Intense uveitis	9·66 ± 1·7 µg/ml
(2) Mild uveitis	4·13 µg/ml

* From Cotlier *et al.* (1975). † From Secchi *et al.* (1976b)

The increased level of LPC in aqueous humour during inflammation may be due to a breakdown of the blood-aqueous barrier for phospholipids (Cotlier *et al.*, 1976). We would point out, however, that an enhanced activity of phospholipase A may be responsible for an increase of lysophosphatidyl choline from cell membrane phosphatidyl choline. Phospholipase A activity, in fact, is enhanced during inflammation (from lysosomes and mast cells) and is thought to increase also during the final steps of the complement sequence.

The same phospholipase may also be responsible for a release of arachidonic acid from membrane phospholipids and, through a cyclic peroxide, for the synthesis of prostaglandins (PGE$_2$ and PGF$_{2\alpha}$. The level of prostaglandins in fact has been shown to increase in the aqueous humour during experimental or clinical uveitis. The effect of prostaglandins on the lens permeability has been investigated (Paterson and Eck, 1973), but the experimental results have shown that a derangement in the normal lens permeability may take place in vitro only when prostaglandins are present in the reaction medium at far higher concentrations than those found in the aqueous humour during inflammation.

Whether the rise of LPC in the aqueous is due to a breakdown of the blood-aqueous barrier and/or to an increase of phospholipase A activation, the fact remains that aqueous humour during inflammation, either experimental or clinical, contains 'factors' which are potentially cataractogenic. Moreover, the same factors may induce a leakage of soluble proteins from the lens in the surrounding media. These proteins have been shown to be immunogenic (Lanzieri and Secchi, 1965; Rahi *et al.*, 1977) as 'sequestered antigens' and, thus, potential cause of inflammation when in contact with immunocompetent tissue.

The finding of antilens antibodies in the aqueous humour during uveitis is well established (Witmer, 1964; Luntz, 1968; Secchi *et al.*, 1976a), and the development of a cell mediated immunity to the lens in the course of anterior uveitis has been reported by Henley *et al.* (1974). It is conceivable that both humoural and cellular immunity to the lens is the result of a leakage of immunogenic material from the lens itself.

Soluble lens proteins in the aqueous during inflammation have seldom been looked for, though Sandberg *et al.* (1974) showed a significant presence of α-cristallin in human aqueous from eyes with Fuchs syndrome.

The rise of LPC in the aqueous humour during inflammation may therefore be relevant not only in the development of complicated cataracts in uveitis but also in the pathogenesis of recurrent anterior non-granulomatous uveitis, which to some extent would be phakogenic.

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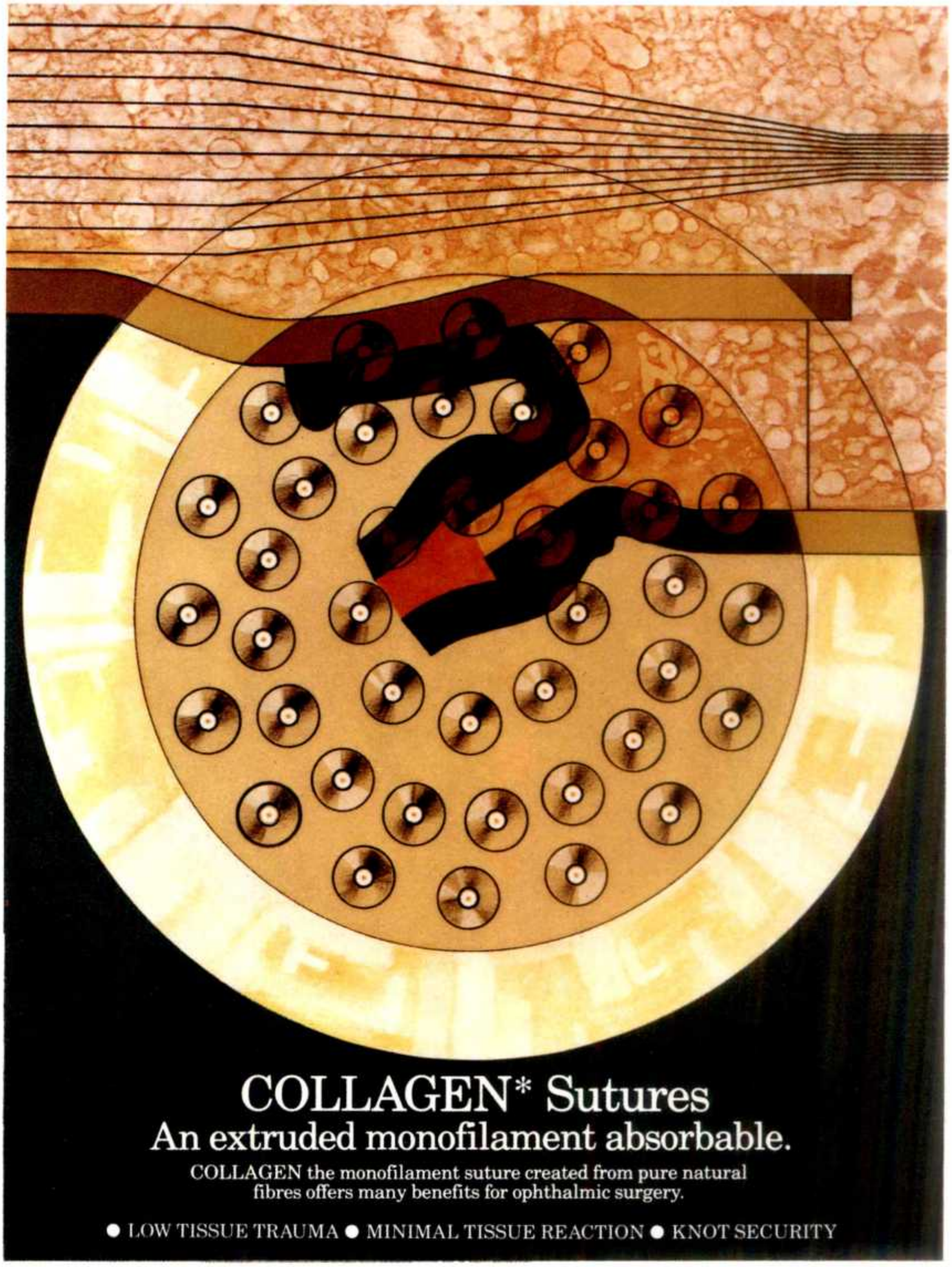

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British Journal of Ophthalmology, 1979, **63**, 771–778

Management of subluxated and dislocated lenses with the vitrophage

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SUMMARY Thirty-two eyes with subluxated and dislocated lenses were surgically managed by means of the vitrophage. The best results were obtained for those cases in which subluxation or dislocation of lenses into the vitreous was not associated with other complications such as glaucoma, perforating injuries, and retinal detachment. No major intraoperative or postoperative problems were seen in uncomplicated cases during a follow-up period ranging from 5 to 45 months.

Management of subluxated and dislocated lenses has remained controversial. The indications for surgical intervention and the procedure of choice are still debatable. Many indications for the removal of dislocated lenses have been described (Haik, 1961; Chandler, 1964; Selleyer and Barraquer, 1973). However, these vary among surgeons. Surgical techniques previously used for removing subluxated or dislocated lenses have included discission, aspiration, lens extraction with forceps or loop, and cryoextraction. Unfortunately these procedures have been associated with a high incidence of operative and postoperative complications (Jarrett, 1967; Barraquer, 1972; Liesman, 1972), such as vitreous loss, retinal detachment, and glaucoma. For this reason many ophthalmologists have considered surgery for dislocated lenses to be very risky and have avoided operating on such eyes.

The automated vitrectomy instruments such as the vitrophage have greatly aided the surgery of the anterior segment. We have previously described the use of this instrument for cataracts in adults and children, for anterior segment reconstruction (Peyman and Sanders, 1975; Peyman, *et al.*, 1975; Peyman *et al.*, 1977; Peyman *et al.*, 1978a, b) and for removal of dislocated lenses through the pars plana route (Peyman and Sanders, 1975). In this report we describe various techniques we have used to deal with dislocated lenses of different types.

Materials and methods

The surgical management of ectopia lentis depends on the dislocation site and the consistency of the lens. A total of 32 such eyes (27 patients) were referred to the Vitreous Service of the University of Illinois Eye and Ear Infirmary between 1974 and 1978. These cases were divided into 6 categories, because the management and prognosis varied according to the clinical aspects of each group.

Group a—Subluxation of soft lens behind the pupil. This group was composed of 10 eyes (6 patients). Two patients had Marfan's syndrome; in the rest the subluxation was of unknown aetiology. Except for 1 patient age 30 all were younger than 17 years (range 5–16). All eyes were uninflamed and normotensive. The indications for surgical intervention were impaired vision in 8 eyes and annoying diplopia in 2.

Group b—Dislocation of soft lens into the vitreous. In 12 eyes (12 patients) there was total dislocation of the lens into the vitreous. All had a history of trauma. One patient had diabetes mellitus, and another had a positive serological test result for syphilis. Five eyes had clear corneas and normal intraocular pressures. The other 7 patients had raised intraocular pressures. Of these 7 patients 5 had angle recession and 2 had phacolytic glaucoma. The indications for surgery were raised intraocular pressure in 7 eyes and vitreous opacities in 5 eyes.

Group c—Dislocation of hard lens into the vitreous. Only 1 patient was in this category. An 80-year-old patient fell and dislocated a mature cataract in 1 eye. The cornea showed 1+ oedema, intraocular pressure was high, and the vitreous had a marked reaction, possibly due to leakage of lens material.

Group d—Lens dislocation associated with perforating ocular injuries and severe ocular trauma. Five eyes (5 patients) had lens dislocation due to perforating corneoscleral injuries. All had total

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detachment of the retina and vitreous haemorrhage. Because of the extensive nature of the ocular trauma these eyes were considered virtually lost preoperatively.

Group e—Dislocation of soft lens into the anterior chamber. Two eyes (2 patients) had a dislocation of the lens into the anterior chamber. Both patients had aniridia, corneal oedema and dystrophy, and raised intraocular presure.

Group f—Dislocation of hard lens into the anterior chamber. One patient with tertiary syphilis had bilateral dislocation of hard lenses into the anterior chamber with corneal oedema and raised intraocular pressure.

SURGICAL TECHNIQUES

Group a—Technique of pars plicata lensectomy and vitrectomy for soft subluxated lenses. Sutures are passed through the lid margins for exposure. Then 4-0 silk traction sutures are placed beneath the bellies of the four rectus muscles. A radial peritomy is made in the inferotemporal or superotemporal quadrant and extended in a T-shaped manner along the limbus toward the inferior and lateral recti. After cauterising the episcleral bleeding points, a 4-mm long sclerotomy bed 2·5 to 3 mm from the limbus is prepared with a No. 15 Bard-Parker blade. When the underlying ciliary body is exposed, it is gently cauterised. A mattress suture is passed through the lips of the sclerotomy and a loose double-throw knot is applied. Either 4-0 or 5-0 polyglactin 910 (Vicryl) or Supramid suture material can be used for this purpose.

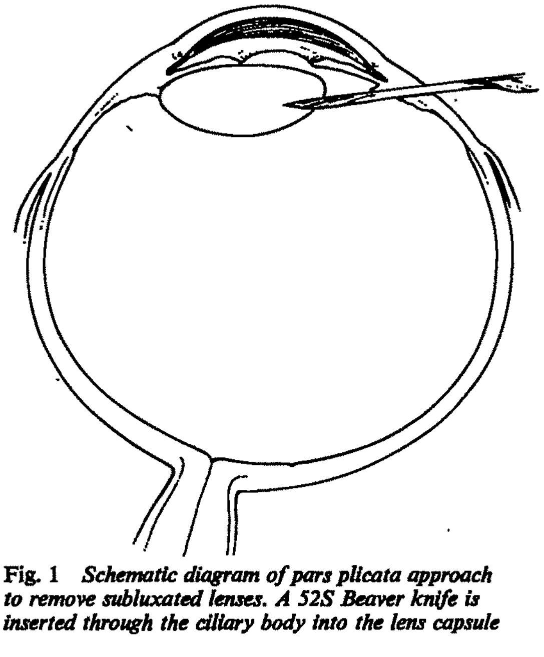

Fig. 1 *Schematic diagram of pars plicata approach to remove subluxated lenses. A 52S Beaver knife is inserted through the ciliary body into the lens capsule*

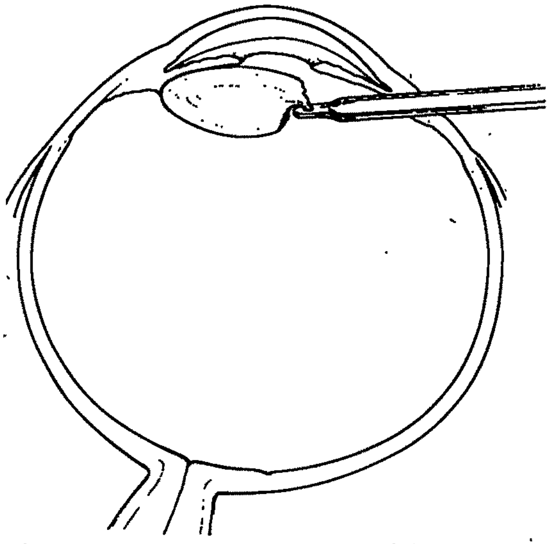

Fig. 2 *Vitrectomy instrument is inserted through the knife tract and the soft subluxated lens is removed*

A 52S Beaver blade is passed through the sclerotomy and through the pars plicata into the lens equator, and a track in the lens is made by means of slow slicing motions of the blade. The blade is removed and a wide angle cutter vitrophage (Figs. 1 and 2) is introduced through the sclerotomy into the lens. The mattress suture at the sclerotomy is tightened.

The lens material is cut and removed by the cutting/aspirating tip of the vitrophage. It is essential that the cutting tip is always visible in the pupillary axis. The lens material that is lying behind the iris or ciliary body is brought into the operator's view by indenting the corresponding sclera with a finger tip or cotton-tipped applicator. With the suction function of the vitrophage lens material is brought into view and then cut. The cutting action of the vitrophage is activated only when the cutting port of the vitrophage is in view. This manoeuvre avoids cutting the iris or ciliary processes accidentally. After the lens is removed an anterior vitrectomy is done. At this point a self-infusing fundus contact lens is placed on the cornea. A deep vitrectomy to the optic disc is done. Any lens particles that may have fallen into the vitreous accidentally can easily be retrieved. After completion of the vitrectomy the vitrophage is removed and the sclerotomy suture is tied. Conjunctiva is sutured with 6-0 plain catgut. Atropine and Maxitrol (neomycin and dexamethasone) drops are instilled, and a patch and shield are applied to the eye.

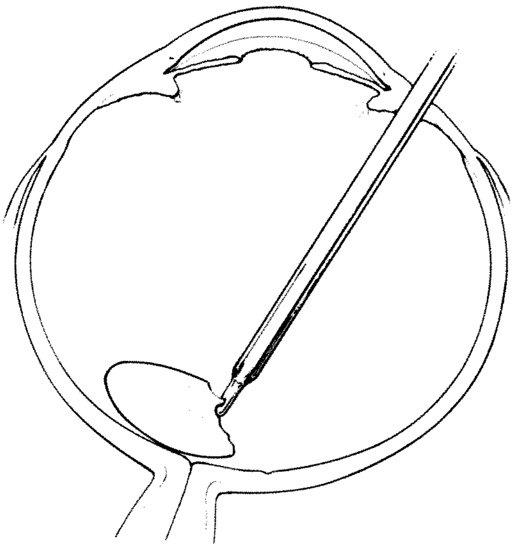

Fig. 3 *Schematic diagram of removal of a dislocated soft lens with the vitrophage*

On a routine basis an iridectomy (either peripheral or sector) is not necessary. However, when the pupil does not dilate well, a small sector iridectomy can be performed with the cutting action of the vitrophage.

Group b—Management of dislocated soft lens into the vitreous. When a soft lens is dislocated into the vitreous or is lying on the surface of the retina, the initial steps of the technique are the same as for group *a*.

After the vitrophage is inserted into the vitreous cavity an anterior vitrectomy is performed, and the vitreous surrounding the lens is removed. By applying suction it is possible to lift the lens and bring it to the pupillary area, where it can be cut away under direct visualisation (Fig. 3).

At times, in addition to the vitrophage tip, a 25-gauge needle (1½ inches long) (3·8 cm) is inserted through the pars plicata at the opposite side of the initial sclerotomy incision (Peyman and Sanders, 1975) (Fig. 4). The lens can be lifted with the tip of the needle, brought into the pupillary area, and removed by the vitrophage.

Group c—Management of hard dislocated lens in vitreous. When the nucleus of the subluxated or dislocated lens is very hard, as in older patients, it is inadvisable to attempt removal of the lens through a posterior approach. These lenses are best removed through a clear corneal incision. The technique involves lifting the dislocated lens with a needle and bringing it into the anterior chamber. The assistant holds the lens pierced by the needle in this position (Figs. 5 and 6). The assistant also holds the vitrophage in place while infusion is running to prevent collapse of the eye. Then the surgeon performs a clear corneal incision. The lens can be either expressed transcorneally or removed by a cryoprobe.

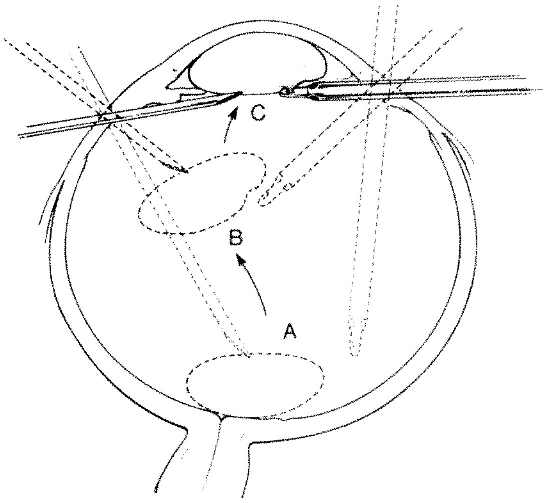

Fig. 4 *Two-needle technique of removing lenses of 1 to 2+ nuclear sclerosis. The needle stabilises the lens while it is cut with the vitrectomy instrument.* A. *After vitrectomy a 25-gauge needle engages the dislocated lens.* B. *Lens in midvitreous supported by the needle and vitrophage.* C. *Lensectomy performed*

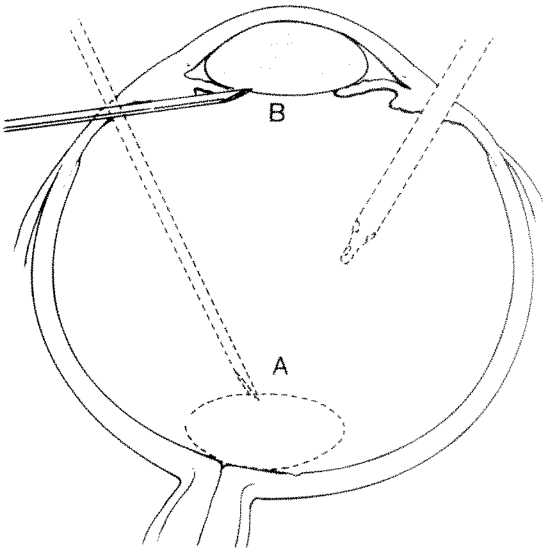

Fig. 5 *Removal of dislocated hard lens.* A. *After vitrectomy the lens is lifted with the tip of a 25-gauge needle.* B. *Lens is brought into the anterior chamber*

The vitrophage is kept in the eye while this occurs. By keeping the eye infused intraocular pressure can be easily re-established. After closure of the corneal incision (with 9-0 nylon), a vitrectomy is performed (Fig. 7). If the lens is ruptured, lens fragments or capsular remnants can be removed with the vitrophage.

Group d—Lens dislocation associated with perforating ocular injuries. The initial step in these cases is to repair the scleral and corneal perforations. A sclerotomy is made in a quadrant that is usually opposite the quadrant in which the perforation has occurred. Vitrectomy is performed to clear the vitreous haemorrhage and to remove the dislocated lens. Once the media are clear, appropriate retinal surgery is performed.

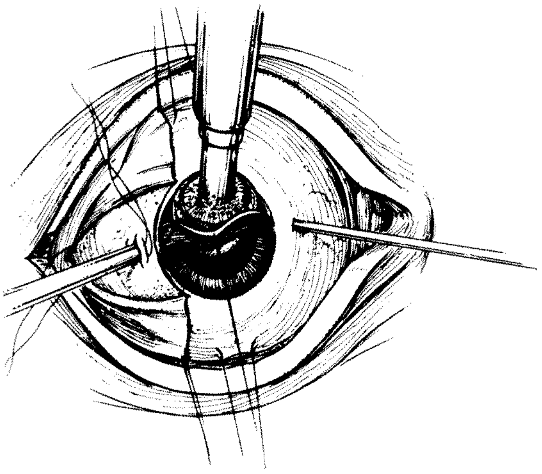

Fig. 6 *The vitrophage and the needle remain inside the eye while the dislocated hard lens is removed through a clear corneal incision with a cryoprobe*

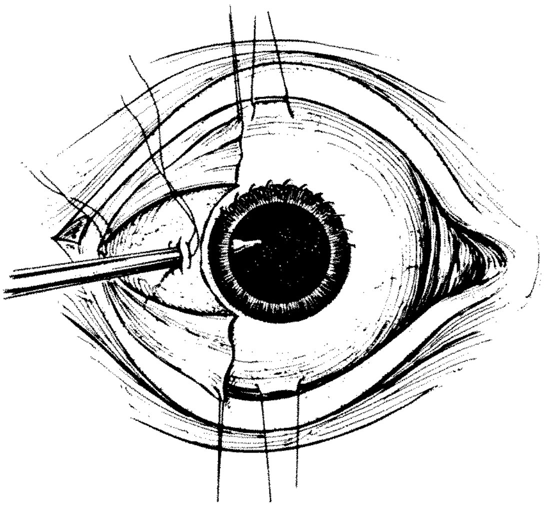

Fig. 7 *After closure of the corneal wound and removal of the 25-gauge needle the vitrectomy is completed*

Group e—Dislocation of soft lens into the anterior chamber. A standard sclerotomy is made in the inferotemporal or superotemporal quadrant, and the vitrophage is inserted as described for group *a.* The pupil should be well dilated so that the vitrophage tip has access to the anteriorly dislocated lens. With the wide angle cutter vitrophage the lens is cut and removed. Then a vitrectomy is performed from the iris plane back to the optic disc.

Group f—Dislocation of a hard lens into the anterior chamber. When the crystalline lens is hard and dislocated into the anterior chamber, it is better to remove it through a corneal incision. A standard sclerotomy is performed before the removal of the lens. This is a helpful step, because the eye may collapse during extraction of the lens due to vitreous loss. To perform sclerotomy on a collapsed eye is difficult, and insertion of a vitrectomy instrument through such a sclerotomy can cause detachment of the ciliary body and choroid. After insertion of a 52S Beaver knife through the sclerotomy into the vitreous the sclerotomy is closed temporarily and a clear corneal incision or another type of limbal incision is made. The lens is then removed. After suturing the corneal incision the sclerotomy is opened and a vitrectomy from the iris to the optic nerve is done.

Results

Group a—Subluxation of soft lens behind the pupil. Excellent surgical results were obtained in all 10 eyes (Table 1a). There were minimal operative complications, namely, limited bleeding in 1 case. The postoperative period, except for transient corneal oedema in 2 eyes, was uneventful. Visual improvement was seen in all cases. However, the visual improvement was minimal in 2 eyes due to amblyopia.

Group b—Dislocation of soft lens into the vitreous (Table 1b). Operative results were excellent in the 5 eyes that did not have preoperative glaucoma.

In the 2 eyes with phacolytic glaucoma the intraocular pressure returned to normal between 2 and 3 weeks postoperatively. During that time the intraocular pressure was controlled by medical therapy.

In 5 eyes with angle recession glaucoma the intraocular pressure did not return to normal after surgery. In 2 of these eyes additional surgery was required to control glaucoma; in the other 3 eyes prolonged medical therapy has been necessary. Visual acuity deteriorated in 2 eyes of this group.

Table 1 *Details of cases*

Case number	*Age (yr)*	*Preoperative diagnosis*	*Operative complication*	*Postoperative complication*	*Preoperative visual acuity*	*Postoperative visual acuity*	*Comment*	*Follow-up (mo)*
(a) *Subluxation of soft lens*								
1	8	—	None	None	20/300	20/60	Alternating esotropia	7
2	8	—	,,	,,	3′/200	20/40	,,	7
3	12	—	,,	,,	4′/200	20/50	,,	5
4	12	—	,,	,,	20/400	20/60	,,	5
5	16	Marfan's syndrome	,,	Transient corneal oedema	20/300	20/100	Amblyopia	8
6	7	—	,,	None	20/200	20/80	Alternating esotropia	8
7	7	—	,,	,,	Hand motions	20/70	,,	7
8	5	—	Minimal bleeding	Transient corneal oedema	20/200	20/50	,,	6
9	5	—	None	None	20/200	20/60	,,	6
10	30	Marfan's syndrome	,,	,,	5′/200	20/200	Amblyopia	6
(*b*) *Dislocation of soft lens into the vitreous*								
1	42	Uncontrolled glaucoma, traumatic dislocated lens, vitreous touch, angle recession	Transient corneal oedema	Persistent raised intraocular pressure	Hand motions	Light perception	Trabeculectomy done	45
2	54	Traumatic dislocation, corneal oedema, raised intraocular pressure, angle recession	—	Phthisis	Hand motions	No light perception	Trabeculectomy done	5
3	60	Traumatic dislocation, angle recession, raised intraocular pressure	Mild bleeding	Raised intraocular pressure	Counting fingers	20/70	Intraocular pressure controlled with acetazolamide	9
4	76	Angle recession, traumatic dislocation, raised intraocular pressure, choroidal rupture	None	Transient corneal oedema	Hand motions	20/60	,,	6
5	35	Phacolytic glaucoma, traumatic dislocation	,,	—	Counting fingers	20/100	—	11
6	78	Traumatic dislocation, angle recession, uveitis, raised intraocular pressure	None	None	Counting fingers	20/50	Intraocular pressure controlled with acetazolamide	29
7	54	Traumatic dislocation, phacolytic glaucoma	,,	,,	20/100	20/30	—	8
8	11	Traumatic dislocation	,,	,,	Counting fingers	20/25	—	5
9	32	Trauma, uveitis	,,	,,	Hand motions	20/80	—	5
10	14	Trauma	,,	,,	Hand motions	20/25	—	5
11	38	Trauma	,,	,,	Hand motions	20/70	—	8
12	45	Trauma	,,	,,	Hand motions	Counting fingers	Macular degeneration	16

Continued

Table 1 *continued*

Case number	*Age (yr)*	*Preoperative diagnosis*	*Operative complication*	*Postoperative complication*	*Preoperative visual acuity*	*Postoperative visual acuity*	*Comment*	*Follow-up (mo)*
(c) Dislocated hard lens into the vitreous								
1	80	—	None	None	Hand motions	Counting fingers	Senile macular degeneration	6
(d) Lens dislocation with perforating injuries								
1	32	Corneoscleral laceration, retinal detachment	None	None	Light perception	20/25	—	9
2	13	Corneoscleral laceration, retinal detachment	„	Phthisis	„	No light perception	—	5
3	10	Scleral laceration, dislocated lens, retinal detachment	„	„	„	„	—	5
4	27	Scleral laceration, dislocated lens, retinal detachment	„	„	„	„	—	8
5	59	Corneoscleral laceration, retinal detachment	„	—	„	„	—	9
(e) Dislocation of soft lens into the anterior chamber								
1	61	Aniridia, corneal dystrophy, raised intraocular pressure, cupped disc	None	None	Hand motions	Light perception	—	6
2	28	„	„	„	Counting fingers	2'/200	—	6
(f) Dislocation of hard lens into the anterior chamber								
1	48	Corneal oedema, tertiary syphilis, raised intraocular pressure	None	None	Counting fingers	5'/200	—	10
2	48	„	„	„	Light perception	10'/200	—	10

Group c—Dislocated hard crystalline lens into the vitreous (*Table 1c*). After surgery the intraocular pressure gradually returned to normal during a period of 3 weeks. There were no complications during surgery and the postoperative period. Final visual acuity was only counting fingers owing to senile macular degeneration.

Group d—Lens dislocation associated with perforating ocular injuries (*Table 1d*). Because of the extensive nature of injuries only 1 eye of the 5 could be salvaged. Visual acuity was reduced to no light perception in 4 eyes. Three of these eyes became phthisical.

Group e—Dislocation of soft lens into the anterior chamber (*Table 1e*). Both lenses were removed successfully. Because of the decompensated state of the cornea, raised intraocular pressure, and optic atrophy, visual improvement was minimal in one case and vision worsened in the other case. There were no complications during surgery.

Group f—Dislocation of hard lens into the anterior chamber (*Table 1f*). Visual acuity improved, but improvement was limited because of coexistent corneal pathology and glaucoma. There were no surgical complications.

Discussion

Management of ectopia lentis presents a perplexing problem for many ophthalmologists. There is a continuing debate between proponents of active surgical intervention and advocates of conservative treatment. The latter group cite cases in which dislocated lenses have been tolerated well with maintenance of good vision for many years. Although this is true in many instances, other cases require lens removal for optical purposes or for relief of phacolytic glaucoma.

With the availability of automated vitrectomy instruments the much dreaded complication of vitreous loss and its subsequent sequelae can be avoided. Through a small incision a vitrectomy can be done at the time the lens is removed.

In the past the major concern in management of subluxated and dislocated lenses has been the occurrence of operative and postoperative complications, mainly those due to vitreous manipulation. In a large series reported by Jarrett (1967), for example, there was an incidence of vitreous loss of 41%, and one-third of these eyes became blind. Retinal detachments occurred in about 7% of the cases.

Jensen and Cross (1972) reported a 30% incidence of vitreous loss during surgery in patients with Marfan's syndrome. Surgical techniques included discission, aspiration, and intra- or extracapsular extraction. In one-fourth of these eyes retinal detachment subsequently developed. Similar complications were seen in patients with homocystinuria, and vitreous loss occurred in 30% of these cases. The surgical procedures included aspiration, discission, and intracapsular extraction. Retinal detachment was noted in 11%. Other complications included corneal oedema and iris prolapse. In a large series reported by Selleyer and Barraquer (1973) vitreous loss occurred in 15 of 222 eyes. The surgical techniques used were aspiration and intra- or extracapsular extraction.

The technique of lens aspiration (Maumenee and Ryan, 1969) has been associated with a lower incidence of complications. However, in some cases a secondary discission of pupillary membranes is required. Realising the importance of the vitreous, other surgeons have advocated open-sky vitrectomy before and after lens removal. Croll and Croll (1975), employing open-sky vitrectomy, reported excellent results with cryoextraction of 22 dislocated lenses. Barraquer (1972) also used an open-sky vitrectomy technique to complement cryoextraction.

To avoid confusion we use the term 'subluxation' to imply partial dislocation and 'dislocation' to mean total displacement. In our series excellent surgical results were obtained in all 10 cases of subluxated lenses. There were no significant operative or postoperative complications. In most cases the visual improvement was dramatic. In the eyes where final visual acuity was impaired due to the presence of amblyopia annoying symptoms of monocular diplopia were eliminated.

In our series trauma caused 12 cases of total dislocation of soft lenses into the vitreous. Good surgical results were obtained in 10 eyes. Except for transient corneal oedema and minimal bleeding there were no significant operative complications. Eyes with phacolytic glaucoma returned to normal intraocular pressure after lensectomy and vitrectomy. However, eyes with traumatic angle recession glaucoma did not do so well. Rosenbaum and Podos (1967) reported on a series of 27 cases of traumatic dislocation of lenses. Of these, 15 (56%) had raised intraocular pressure preoperatively. One of these was due to phacolytic glaucoma, and others were due to angle recession and peripheral anterior synechiae. Intracapsular lens extraction was attempted on 13 in this group. There was vitreous loss in 11 cases (84%). Seven eyes (54%) had postoperative vision of counting fingers or less. In Jarrett's series (Jarrett, 1967) there were 31 cases of traumatically dislocated lenses associated with glaucoma. Removal of lenses in 24 eyes led to control of glaucoma in only 6 eyes. The other 7 cases were managed conservatively. Rodman (1963) studied histopathologically a series of eyes that had been enucleated because of glaucoma and a dislocated lens. Postcontusion deformity of the chamber angle was seen in 95% of those eyes that had glaucoma and an open angle. The efficiency of lens removal in the management of angle recession depends therefore upon the state of the angle.

Dislocation into the vitreous of a lens with a hard nucleus occurred in only 1 case in our series. This was successfully removed through a clear corneal incision, while the vitrophage tip was maintained in the vitreous through a sclerotomy.

Our visual results were poor when lens dislocation was associated with perforating injuries, although vitrectomy and lensectomy helped to clear the media and reform the globes. Because of damage to the ciliary body and the retina (often with inoperable retinal detachment), the majority of the eyes could not be saved.

Anteriorly dislocated lenses can be managed through the pars plicata or pars plana if the lens is soft. If the lens is hard, it should be removed through a clear corneal incision. In our series the postoperative results depended on the preoperative status of the cornea and presence of glaucoma or retinal changes. There were no complications as a result of surgery.

We now have postoperative follow-up of subluxated and dislocated lenses for a period ranging from 5 to 45 months. The early postoperative complications were directly related to pre-existing conditions of the eyes, such as corneoscleral laceration, retinal detachment, or uncontrollable glaucoma. We have not observed significant adverse changes late in the follow-up period. Although longer follow-up is desirable, the present results can be considered very encouraging. We believe that a 1-stage pars plicata or pars plana lensectomy and vitrectomy is an ideal procedure for the management of those subluxated or dislocated lenses that require removal.

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Interference of 50 Hz electrical cortical potentials evoked by TV systems

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SUMMARY Application of TV systems for generating patterned stimuli for the examination of the electrical cortical potentials has disadvantages caused by the frame frequency of 50 Hz of TV sets. Apart from a larger variability in latency times of the electrical potentials as compared to the results obtained by projector systems, a 50-Hz noise on the recordings mediated through the visual system may be seen. These disadvantages can be ameliorated by increasing the frame frequency of the TV set.

In a previous paper (van Lith *et al.*, 1978) some disadvantages of the application of television (TV) systems as a stimulus device for evoking electrical cortical potentials (EPs) were discussed. We paid attention mainly to the variability in latency times due to the frame frequency of the TV. Another disadvantage, namely, a 50 Hz interference in the recordings, was mentioned as being present only when the starting points of the visual stimuli were synchronised with frame of the TV screen. The cause of this 50 Hz noise was not discussed because we thought it originated in induction, but the cause of it has since turned out to be different.

Materials and methods

A TV stimulus device, similar except in inessential details to Arden's (Arden and Faulkner, 1977), was applied. Synchronisation of stimulus and frame caused a 50 Hz ripple, which particularly hampered the measurement of small potentials (Fig. 1). Tests to diminish this ripple were carried out with a blank TV screen, without a luminance or patterned stimulus. The field size of the TV screen was approximately 26°. Electrode positions were the same as in the previous paper. The band width of the amplifiers was 0·1 to 100 Hz, and 128 counts were averaged. The 50 Hz noise was investigated further (Figs. 2 and 3) with a band filter of 50 Hz. Experiments were carried out on persons whose recordings always showed much of this 50 Hz noise.

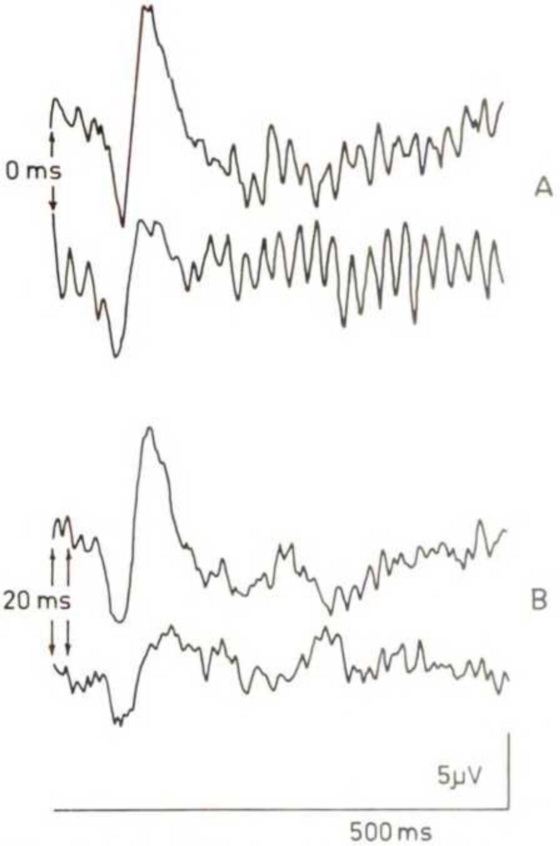

Fig. 1 *EPs to a 1-Hz pattern flash stimulus of 40 ms duration.* (A) *synchronisation between the frame frequency of the TV set and the pattern generator;* (B) *no synchronisation, i.e., the stimulus starts at random within 20 ms. The upper recordings of each pair are from bipolar leads over the occipital lobe, the lower ones are made in reference to the ear lobe*

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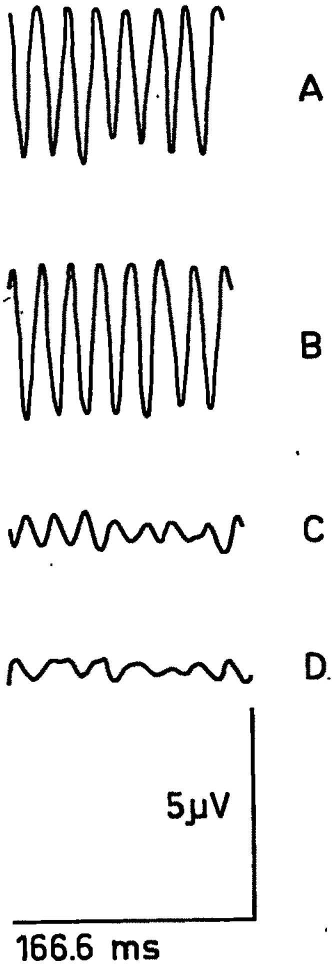

Fig. 2 *50-Hz potentials of approximately 4 μ V, registered from the occipital lobe and provoked by a blank TV screen, synchronised with the averager.* (A) *unshielded;* (B) *electrically shielded;* (C) *visually shielded;* (D) *visually and electrically shielded*

Results

We did not succeed in diminishing the 50 Hz noise by shielding the subject electrically as carefully as possibly (Figs. 2A and B), nor had a 50 Hz notch filter much influence. However, if all the metal shielding was taken away and the eyes were simply closed or a black cloth was held before the screen, the 50 Hz potentials almost entirely vanished (Fig. 2C). Little further improvement was attained when the electrical shields were added. Apparently these potentials were responses mediated through the visual system and not artefacts caused by induction. Further evidence for this inference was obtained by varying the luminance of the screen, which clearly showed the luminance dependence in two subjects (Fig. 3). We called these 50 Hz potentials 'visual hum'.

Discussion

We believe the 2 factors responsible for the variable latency times (van Lith *et al.*, 1978) also cause the visual hum. These 2 factors were the sequential lighting up of the TV screen every 20 ms and the small EP visual field—that is, the part of the visual field from which the EPs are mediated.

The picture on a TV screen is built up by a light point which runs over the screen in 20 ms. When the light point is outside the EP visual field, the screen is dark for the electrode which records the evoked potential. When the light point runs inside the EP visual field, the screen lights up in relation to the electrode placed over the visual cortex. This implies that every 20 ms, that is, 50 times per second, the electrode over the cortex sees a light stimulus and registers an evoked potential, at least if the 50 Hz flicker is below the critical fusion frequency (CFF) of the visually evoked cortical potentials.

Data about the latter can be obtained from a

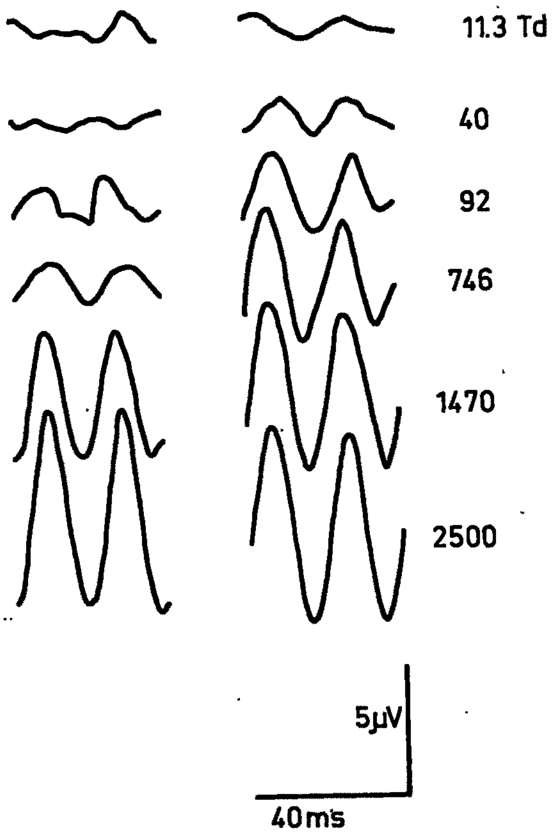

Fig. 3 *Dependence of the 50-Hz potentials ('visual hum') on retinal illumination*

paper by Kelly (1964), which states that the CFF of EPs is just below or over 50 Hz, the result being dependent on retinal illumination. This means that 50 Hz is a critical frequency, which it also appears to be from the results in our tests. Some of our patients transmit the 50 Hz to the registering electrode, others do not. Since it is caused by a characteristic of TV systems, visual hum will not be present when projector systems are used.

When using a TV system there are 2 ways to get rid of visual hum, namely, by lowering the mean luminance of the screen, though this will depress the height of the EPs too and will lengthen the latency time, and by increasing the frame frequency of the TV set. The latter solution will also decrease the variability in latency time.

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Rebound nystagmus: EOG analysis of a case with a floccular tumour

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SUMMARY Eye movements were recorded and quantitatively analysed in a patient with a tumour initially involving the cerebellar flocculus. Ocular motor abnormalities included (1) impaired smooth pursuit, (2) impaired cancellation of the vestibulo-ocular reflex when fixating an object rotating with the head, and (3) gaze paretic and rebound nystagmus. Comparable findings have been reported in monkeys with experimental floccular lesions. The rebound nystagmus (but not the other ocular motor abnormalities) disappeared when the tumour appeared to invade the brain stem in the region near the vestibular nuclei. This finding suggests that the floccular lesion unmasked a bias which created rebound nystagmus and that the bias probably arose in the vestibular nuclei.

Rebound nystagmus refers to a transient nystagmus that occurs when a patient returns the eye to the primary position after a prolonged attempt at eccentric gaze. Slow phases are in the direction of prior attempted eccentric gaze. It has been suggested that rebound nystagmus reflects a transient bias that has been created by the central nervous system in an attempt to hold eccentric gaze (Hood *et al.*, 1973; Zee *et al.*, 1976). Rebound nystagmus occurs even in normal individuals if, after a prolonged attempt at holding eccentric gaze, they return their eyes to the primary position in darkness (Zee *et al.*, 1976). Darkness prevents the visual stabilisation systems from nulling the bias that causes rebound nystagmus. Therefore the bias of rebound nystagmus may be a normal compensatory phenomenon. In patients then rebound nystagmus appears in the light as well, because their visual stabilisation systems (that is, smooth pursuit) are impaired.

Hood *et al.* (1973) described rebound nystagmus as a useful sign of disorders of the cerebellum. However, it is not yet known where the bias of rebound nystagmus is created (Sharpe, 1974). Recently we observed a patient with a presumed floccular-nodular lesion who had gaze paretic and rebound nystagmus. However, the rebound but not the gaze paretic nystagmus disappeared when the tumour extended into the brain stem in the region of the root entry zone of the vestibular nerve, brachium pontis, and vestibular nuclei. We report a detailed oculographic analysis of this patient's eye movements before and after several operations.

Methods

Electro-oculograms (EOG) of horizontal eye movements were recorded with a high-impedance direct current amplifier coupled to silver-silver chloride electrodes fixed at points lateral to both outer canthi. The eye position signal was also electronically differentiated to obtain eye velocity. Analogue signals were displayed on a rectilinear pen writer. The overall band width of the recording system was 30 Hz.

The ocular motor examination consisted of the following. (1) Fixation behaviour: fixation in the primary position, eccentric fixation, and fixation in primary position after a prolonged attempt at holding eccentric gaze (to elicit rebound nystagmus). (2) Smooth pursuit: pursuit gain (smooth eye velocity /target velocity) was measured as the eye passed through the primary position while the patient tracked a small target moving in a triangular wave fashion. (3) Vestibulo-ocular responses: vestibular nystagmus was elicited by rotating the patient en bloc in a Bárány chair in complete darkness. Mental arithmetic was used to maintain a constant mental state. Cancellation of the vestibulo-ocular reflex (VOR) was measured as the patient attempted to fixate a target rotating with her. Standardised hot and cold water caloric tests were performed with eyes open behind +30 lenses. The maximum

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slow phase velocity and duration of the induced nystagmus was calculated. Canal paresis was defined by the following formula: If (30°C left + 44°C left) — (30°C right + 44°C right) was greater than 40 seconds a canal paresis was indicated. (4) Saccades: saccadic eye movements were measured during tracking of a target jumping in a nonpredictable stepwise fashion.

Case report

A 17-year-old woman came to the Department of Ophthalmology with the complaint of oscillopsia of 1 week's duration. She also had a 10-month history of headaches. Neurological examination showed questionable papilloedema but apart from the abnormalities of eye movement no other neurological findings. On clinical ocular motor examination she showed striking gaze paretic and rebound nystagmus as well as abnormal smooth pursuit. Fig. 1 shows a horizontal EOG recording of her nystagmus. In the primary position fixation was steady. On assuming eccentric gaze in either horizontal direction she showed gaze paretic nystagmus with a slightly decreasing slow-phase velocity wave form (Holmes, 1917; Zee *et al.*, 1976), which diminished as she maintained eccentric fixation. The initial slow-phase velocity of gaze paretic nystagmus during attempted rightward fixation was higher than that during attempted leftward fixation. On return to the primary position rebound nystagmus appeared.

Fig. 2 shows the patient tracking a target moving in a triangular wave fashion. Smooth pursuit movements were bilaterally impaired necessitating catch-up saccades. However, the gain (smooth eye velocity/target velocity) for rightward tracking was less (0·21) than that for leftward tracking (0·71).

Fig. 3 shows the patient attempting to cancel her vestibulo-ocular reflex using a small fixation target rotating with her head. Normally cancellation is complete and fixation is steadily maintained. However, the patient was unable completely to cancel her vestibulo-ocular reflex, so the eyes were taken off target by the vestibular slow phase requiring her to make saccades in order to reacquire the target. Cancellation during rightward head rotation was more severely affected (gain (eye velocity/head velocity) = 0·53) than during leftward head rotation (gain = 0·10).

Caloric testing showed normal responses in both ears. Saccadic eye movements showed normal accuracy and velocity-amplitude relationships.

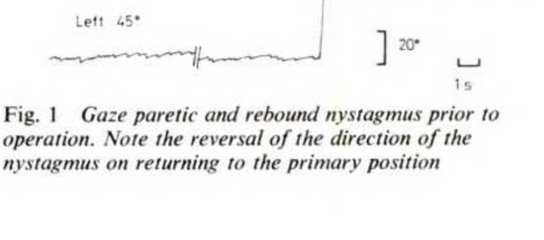

Fig. 1 *Gaze paretic and rebound nystagmus prior to operation. Note the reversal of the direction of the nystagmus on returning to the primary position*

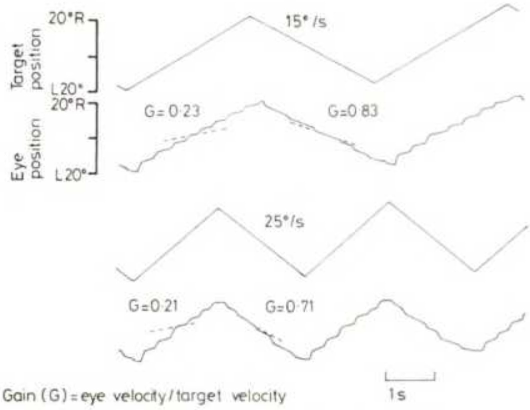

Fig. 2 *Bilateral abnormality of smooth pursuit movements before operation. Pursuit gain showed asymmetric disturbance (rightward gains were less than leftward gains)*

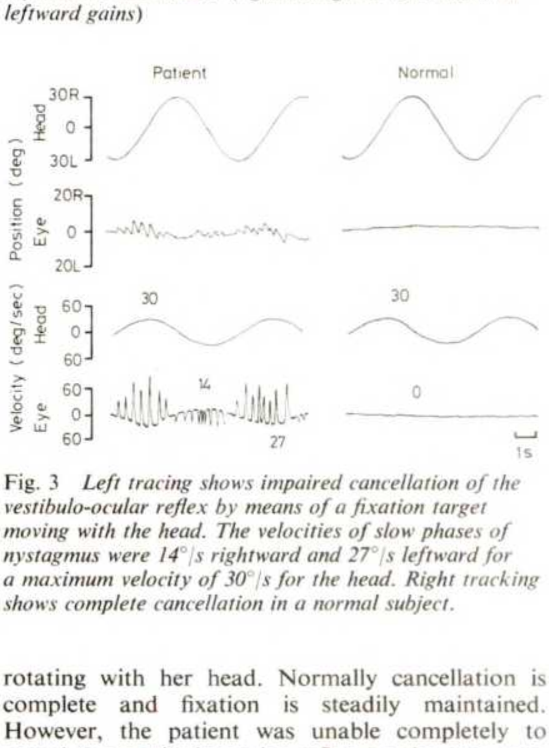

Fig. 3 *Left tracing shows impaired cancellation of the vestibulo-ocular reflex by means of a fixation target moving with the head. The velocities of slow phases of nystagmus were 14°/s rightward and 27°/s leftward for a maximum velocity of 30°/s for the head. Right tracking shows complete cancellation in a normal subject.*

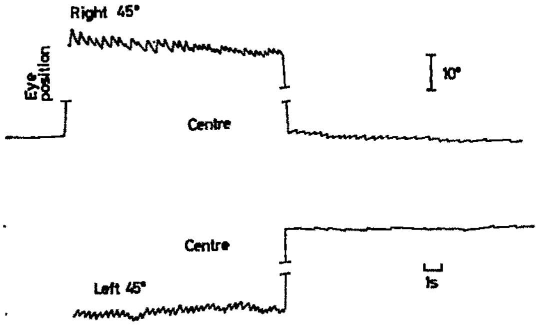

Fig. 4 *Gaze paretic and rebound nystagmus after the first operation in which a tumour involving primarily the right vestibulocerebellum was removed. When gaze was directed towards the side of tumour (to the right), there was a large-amplitude gaze paretic nystagmus, whereas on gaze left a small-amplitude nystagmus appeared. Note the differences in duration and amplitude of nystagmus between right and left gaze*

Neuroradiological studies suggested a mass in the posterior fossa, and the patient underwent a suboccipital craniotomy. A choroid plexus papilloma was found in the fourth ventricle involving the right flocculus, nodulus, part of the right cerebellar hemisphere, and a part of the left flocculus as well. The tumour was partly removed together with a portion of the right flocculus and paraflocculus.

After this operation the pursuit deficit and gaze paretic and rebound nystagmus persisted (Fig. 4). However, the abnormalities were more marked, especially on rightward gaze.

Two months later, just before reoperation in an attempt to remove the remaining part of the tumour, the patient was again examined. Gaze paretic nystagmus and impaired pursuit were still present. However, she no longer had rebound nystagmus. At the second operation residual tumour was found in the region of the right flocculus and nodulus as well as involving the brain stem at the juncture of the right vestibular nerve and brachium pontis. As much tumour as possible was removed.

Fig. 5 shows an EOG recording 20 days after the second operation. In the primary position there was a small-amplitude jerk nystagmus with slow phases to the right. This increased on gaze left. In addition on rightward gaze there was prominent gaze paretic nystagmus. This combination of gaze paretic nystagmus to the right and vestibular nystagmus to the left is so-called Bruns nystagmus (Bruns, 1908; Cushing, 1921). On return to the primary position after prolonged eccentric gaze there was no change in the slow-phase velocity of the primary position jerk nystagmus. In other words rebound nystagmus was no longer present.

At this time caloric testing showed a definite canal paresis on the right side but a normal response on the left side. Fig. 6 shows an EOG recording of the cold water caloric-induced nystagmus. The maximum slow-phase velocity of nystagmus and the duration of responses showed a clear asymmetry, that is, a canal paresis on the right side. Saccadic eye movements were accurate and had a normal velocity-amplitude relationship.

One year after the second operation the patient was re-examined. Now there was no primary-

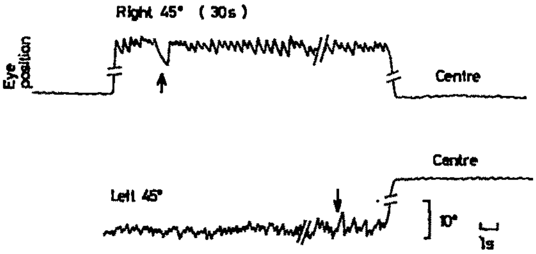

Fig. 5 *Recording of horizontal eye movements after second operation in which the tumour was found to involve the brain stem. In the primary position a small-amplitude jerk nystagmus with slow phases to the right is present. When gaze was directed towards the side of the tumour (right), there was a large-amplitude nystagmus showing an exponentially decaying centripetal drift velocity (↑); on gaze left a small-amplitude, rapid nystagmus exhibiting slow phase of constant velocity (↓) appeared. On return to the primary position no change in velocity of the primary-position nystagmus was noted*

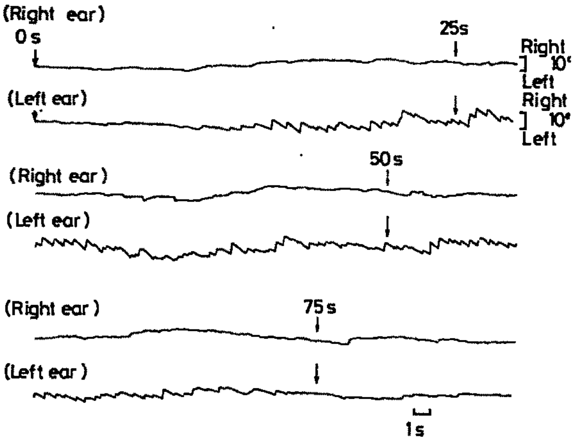

Fig. 6 *Recording of 30°C water caloric-induced nystagmus after the second operation. The maximum slow-phase velocity and duration of the induced nystagmus by the right-ear stimulus were significantly decreased compared with the induced nystagmus by the left-ear stimulus*

position jerk nystagmus, though on caloric testing the right canal paresis persisted. Gaze paretic nystagmus and the smooth pursuit deficit were still present, and rebound nystagmus had reappeared. There were no signs of tumour recurrence.

Discussion

Our findings suggest that many of our patient's ocular motor abnormalities—gaze paretic and rebound nystagmus, impaired smooth pursuit, and cancellation of the vestibulo-ocular reflex—were related to tumour involvement of the cerebellar flocculus and possibly nodulus. In fact the constellation of ocular motor abnormalities shown by our patient has been reproduced in monkeys with bilateral floccular ablations (Zee *et al.*, 1978). However, our patient's rebound nystagmus (but not the other ocular motor findings) disappeared when the brain stem and in particular the region of the vestibular nuclei, eighth nerve, and brachium pontis appeared to be involved. This finding suggests that the bias that creates rebound nystagmus is developed in the brain stem and not in the flocculus. In fact, the floccular lesion, by causing gaze paretic nystagmus and impairing smooth pursuit, acted as the stimulus to create the need for the production of a bias to counteract the centripetal drift of gaze paretic nystagmus. This bias manifests itself as rebound nystagmus. Of course other extra-floccular, cerebellar structures might be essential for the normal function of the brain stem network that creates the bias of rebound nystagmus.

One might next ask by what mechanism the bias of rebound nystagmus is created. Normally after a saccade the eye is held in its new position by the tonic output of a brain stem neural network that provides the appropriate position coded information for the ocular motor neurons to hold positions of gaze. This gaze-holding neural network has been termed a neural integrator, since functionally it mathematically integrates velocity into position-coded information (Robinson, 1974). There are presumably 2 horizontal neural integrators (one for rightward and the other for leftward movements) that work reciprocally in a push-pull fashion. If the neural integrators become defective, eccentric gaze cannot be held, and the eye drifts back toward the primary position with an exponentially decaying velocity. In an attempt to maintain eccentric fixation repetitive eccentric saccades are required, resulting in the pattern of gaze paretic nystagmus. However, if the defect is symmetrical, a null region exists near the primary position of gaze where fixation is steady.

The centripetal drift of gaze paretic nystagmus causes movement of images across the retina which impairs visual acuity. What adaptive mechanisms are available to the central nervous system to null gaze paretic nystagmus so as to improve visual acuity?

The smooth pursuit system could be used to detect the movement of images on the retina caused by centripetal drift and then promptly generate a motor command in an attempt to track the moving images. This tracking command would be oppositely directed to the direction of eye drift and would in effect null the gaze paretic nystagmus and permit steady fixation. However, in our patient and in most other patients with rebound nystagmus the smooth pursuit system is impaired. Therefore other somewhat slower acting mechanisms must be called upon in an attempt to hold the eyes steady.

Exactly how such mechanisms work or what stimuli bring them into play are not known. The central nervous system might detect the velocity of the continuous centripetal drift of gaze paretic nystagmus by using visual information about retinal slip and/or extraretinal information about eye motion. This stimulus could then be used to produce an oppositely directed *velocity bias* in an attempt to null the drift. Alternatively, the steady state position of the eyes might be monitored and after a prolonged attempt at holding eccentric gaze a *position bias* could be created to shift the null point of the 2 neural integrators towards the direction of attempted gaze holding. Exactly which of these mechanisms are operative in producing rebound nystagmus has not yet been established.

Finally, one must ask why our patient's rebound nystagmus reappeared 1 year after her last operation. Coincident with the return of rebound nystagmus the primary-position jerk nystagmus, presumably of vestibular origin, disappeared even though the caloric responses still showed a canal paresis. One can speculate that the central nervous system's repair mechanisms that rebalanced the vestibular nuclei to eliminate primary-position nystagmus also restored the ability of the brain stem to generate the bias for rebound nystagmus. In fact Haddad *et al.* (1978) have shown that repair of nystagmus after unilateral vestibular nerve lesions can be accomplished without a vestibulocerebellum. However, the reappearance of rebound nystagmus may have simply been coincidental and related to other unknown mechanisms.

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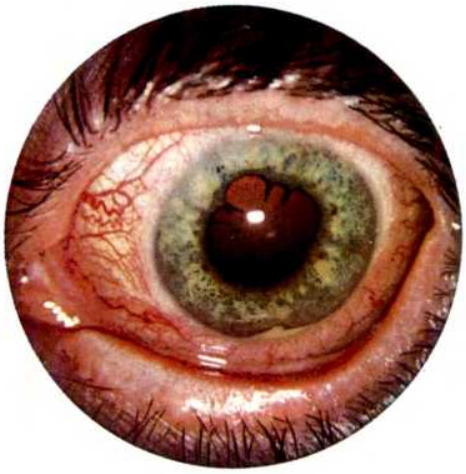

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Use of electroacoustic localisation in the management of intraocular foreign bodies

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SUMMARY A new model of the electroacoustic discriminator and localiser has been put into production, and this paper reports on the preproduction model during its trial period in the management of patients with intraocular foreign bodies. Its particular advantage in localisation at the time of surgery and the procedure for using it are described. The visual results following surgical extraction of 17 cases of magnetic foreign bodies in the posterior segment are outlined.

The success of removing a magnetic foreign body depends on accurate localisation, so that the best surgical approach can be made in each case. We have found the transretinal route of extraction to be the most satisfactory and prefer it to the pars plana route in most cases, as it avoids drawing the foreign body through formed vitreous base. The long-term outcome is good in 80% of cases even if conventional lens surgery is necessary. A pars plana vitrectomy is not required in most cases. The anterior route of extraction has been found to be associated with a high incidence of complications and should not be attempted for posterior segment foreign bodies (Roper-Hall, 1954).

Assessment

The suspicion of a foreign body is aroused by the history and clinical examination, and its nature can usually be ascertained by questioning the patient. Careful clinical examination of the anterior segment may disclose an entry wound, the size of which is a useful indicator of the foreign body size. Similarly, examining the trajectory of the foreign body can be helpful in deciding into which part of the eye the foreign body is likely to have penetrated.

The early clinical assessment should include fundus examination by indirect ophthalmoscopy, which is generally possible if carried out within 24 hours of the injury even if there are advancing lens opacities. At this time a decision on the degree of vitreous haemorrhage present should be made. This finding will significantly influence the future management with respect to the need for vitrectomy. Indirect ophthalmoscopy often reveals the foreign body, but in some 15% to 20% of cases of posterior segment foreign body the view is limited to haemorrhage.

Anteroposterior and lateral *x*-rays are essential whenever an intraocular foreign body is suspected. The preoperative clinical assessment is supported by radiological localisation by the limbal ring method, which we have found to be the most accurate. The relative inexperience of most individual radiographers in general radiological departments makes the occasional *x*-ray localisation less accurate; when the foreign body lies in the posterior segment of the globe, the amount of potential error is considerable. It must be borne in mind that the position of the patient at the time of *x*-ray localisation may be different from that of the operating table. In consequence a mobile intraocular foreign body may come to lie at some considerable distance from its *x*-ray localisation. For this reason both indirect ophthalmoscopy and the procedure of operative localisation with the electroacoustic apparatus described below are used to recheck the *x*-ray findings.

The bewildering array of radiological techniques of localisation which have been described is a measure of their limitations. The author has no personal experience of the image intensifier for localisation. Ultrasonography has proved to be of very limited application in localisation and is no longer routinely used in this hospital.

In doubtful cases the magnetic nature of the foreign body is confirmed before surgery by using the discriminator capability of the apparatus. This clearly avoids a futile surgical operation by an incorrectly chosen procedure.

Electroacoustic discriminator and localiser

The new electroacoustic discriminator and localiser (Fig. 1) is an improved version of the original

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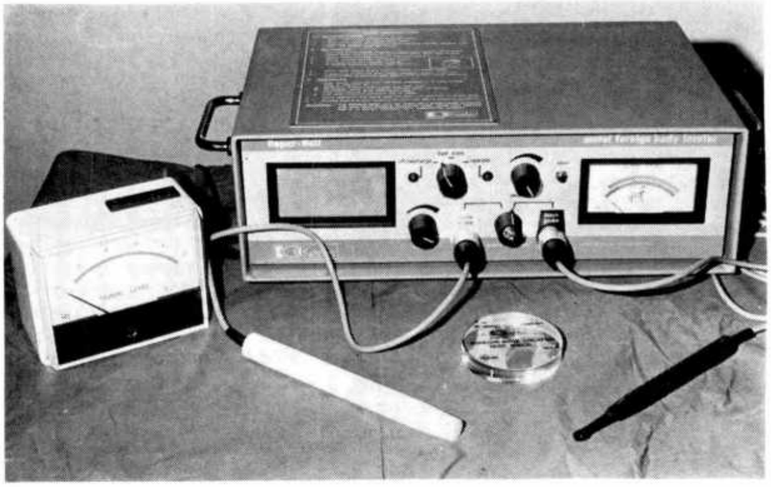

Fig. 1 *The electroacoustic discriminator and localiser*

instrument as devised by Roper-Hall. The electrical principle of its construction is that of a small coil located in a searching probe which is balanced as part of an electrical bridge, the other half of which is remote from the probe head. A magnetic foreign body in the magnetic field of the searching coil causes the magnetic field to intensify and increases the inductance. In the case of a nonmagnetic foreign body the reverse occurs. These alterations in the inductance are recordable on the instrument console both visibly by a needle deflection of the meter and audibly through a loudspeaker. On approaching a magnetic foreign body the increased inductance is converted to an audible high pitched monotone; conversely the reduced inductance caused by a nonmagnetic foreign body is converted to a bleeping sound. Thus magnetic and nonmagnetic foreign bodies are readily distinguished.

Two types of searching probes have been designed. The T probe is by far the more sensitive and its main use is in the detection of minute metallic fragments some of which may have escaped radiological detection or been almost entirely altered by the process of siderosis. The spatula probe has the greatest clinical application and is used both for discrimination, when required, and for localisation at the time of surgical extraction of the foreign body. The instrument is designed to have an effectively limited range, which allows both localisation and freedom from interference by neighbouring metallic structures. The accuracy of localisation is increased by reducing the sensitivity, with a consequent further reduction in range, allowing effective localisation down to zero distance from the foreign body.

Reliability and simplicity of use are the principal attributes of the new apparatus over its predecessor. The storage and operative temperature or humidity do not adversely influence the instrument's sensitivity, so that a high level of operative reliability is attained. Rebalancing the instrument is effected electronically by simply pressing a reset button. The apparatus is powered by a rechargeable battery, which maintains a good reserve of charge. To comply with electrical safety standards the instrument should not be used with direct mains power.

Operative techniques and localisation

With the operating microscope the sclera was exposed through a limbal conjunctival incision, and visibility was improved by muscle traction sutures. Anteroposterior and transverse movements in a serial manner were made on the sclera with the spatula probe (Fig. 2a), initially with the sensitivity raised, but then reduced, until one was satisfied that the foreign body was sited directly beneath the central aperture in the ring head of the probe. This site was then marked. In this series a full-thickness scleral trap approximately 4×4 mm was made (it can be modified according to the expected size of the magnetic foreign body) with a razor blade fragment, and hinged posteriorly to facilitate microscopic visualisation (Fig. 2b). The underlying choroid was cauterised with the hand cautery. Two virgin silk sutures were inserted in the trap. As magnetic force varies approximately with the cube of the distance of the particle to be attracted, powerful magnets are necessary to exert traction from a distance, but a relatively weak instrument is sufficiently effective at close range. The hand-held magnet allows greater local control with continuous microscopic visualisation. Sometimes the giant magnet (Mellinger by choice) was required in cases

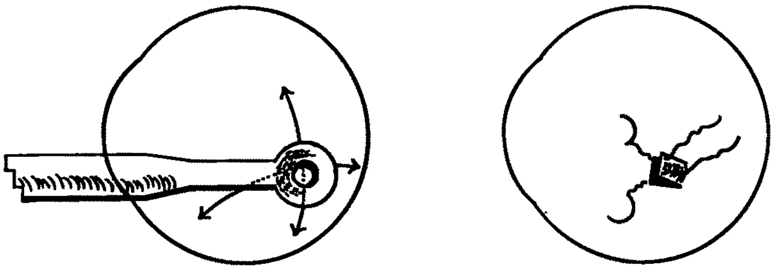

Fig. 2 (a) *Searching movements with spatula probe.* (b) *Posteriorly hinged scleral flap*

of longer standing when a fibrotic reaction might have encapsulated the foreign body.

The extraction was followed by a local vitrectomy at the extraction site and cleansing of the wound margins with hyaluronidase-soaked microsponges. The scleral trap was then repositioned, and additional sutures were inserted to effect sound closure. Cryotherapy was not routinely applied because the combined influence of the foreign body and its operative extraction have been found to exert an adequate reaction locally.

Most foreign bodies can be removed with the technique described. The difficult ones are those which are impacted in the region of the posterior pole. If discrimination confirms a nonmagnetic foreign body, the approach is different and generally necessitates an immediate removal, with vitrectomy.

Results

In 18 cases in which the preproduction model was used it successfully localised 17 foreign bodies within the posterior segment at surgery, and all were extracted as described. In the other case the foreign body was found to have passed through the posterior sclera.

Five of the patients were transferred from other ophthalmic departments; in 3 cases they were referred to this centre because of inadequate local operative facilities. Two patients were referred because of failure to extract the foreign body. The initial failed attempt at surgical removal appears to have been attributable to innaccurate localisation. In both cases accurate electroacoustic localisation led to extraction of the foreign body by the method described.

In this series 7 patients required lens surgery. The overall visual acuity was good in 14 cases. Nine patients retained a visual acuity of 6/6 or better, and an additional 3 patients recovered to 6/9 vision. Arrested lens opacities in 2 patients resulted in a visual acuity of 6/18 in each eye. In 4 patients the visual result was 6/60; the poor visual outcome in 3 of these eyes was due to a combination of macular trauma and extensive vitreous haemorrhage; the presence of siderosis in a long-standing intraocular foreign body resulted in poor vision in 1 other patient.

ADDENDUM. In the production instrument some changes and additional features have been incorporated. A foot-operated reset switch plus an additional mobile meter which can be conveniently situated for the surgeon relieve him of the need to depend on an assistant during the foreign body localisation on the operating table. A pencil probe with a similar range and sensitivity has supplanted the T probe. An extra large probe with a longer range is included; it allows the apparatus to be used in surgical operations on other parts of the body. The spatula probe remains the mainstay of operative ophthalmic localisation. The spatula probe alters the tone signal by a full octave in accordance with whether the foreign body lies in front of or behind the approaching probe. This facility can prove helpful in localising a metallic fragment in a large muscle mass or body cavity. In the localisation of ophthalmic foreign bodies it can be especially helpful in positions of limited exposure in establishing whether a foreign body lies impacted within the sclera and eye or is in the orbital tissues. The rechargeable battery in the production model has a longer charge, which provides about 18 hours of use.

I thank the consultant surgeons at the Birmingham and Midland Eye Hospital for permission to study their patients. My thanks are also due to Mr R. Hildred for photographic assistance and to Mr W. R. Hollingsworth for his advice on the technical descriptions.

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British Journal of Ophthalmology, 1979, **63**, 790–793

Keratoconus, keratoplasty thickness, and endothelial morphology

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SUMMARY A group of successful keratonic grafts (51 eyes) up to 10 years from operation were examined to establish a relationship between graft thickness and acuity. Best acuity occurred in the grafts of normal corneal thickness. No grafts were thinner than normal: thus no tendency to keratonic thinning occurred. No relationship between age of graft and thickness was determined. Endothelial cell studies in vivo of a small number of grafts showed that cell counts a third of normal coexisted with normal acuity and corneal thickness.

It has been suggested that the keratoconus graft can after a time show keratonic features of the primary disease. The present work measured the corneal graft thickness in 51 eyes to establish whether after a time the graft became abnormally thin. According to Ruben (1972) many grafts were thicker than normal cornea, and the greater the thickness the more abnormal the corrected acuity was likely to be. These findings were assumed to be related to endothelial dysfunction and/or stromal fibrosis and corneal irregularity.

In the present study the grafts were only of keratonic eyes and graft eye groups were compared as to their thickness and keratometry. Further, for a few patients with acuity corrected to normal the endothelial mosaic was studied by means of slit-lamp macrophotography and any correlation with corneal thickness was noted. A study of the same group of patients as to acuity, contact lens wear, and effects on curvatures and corneal sensitivity is reported separately (Rubens and Colebrook, 1979a, b).

It is accepted that at the time of operation the fresh donor cadaver material is almost always thicker than normal cornea, and that often during the operation procedure both thinning and clearing of the graft does occur. While this may not be indicative of endothelial function, but rather the drying of the graft, it will be expected that after several years the clear grafts would vary according to the degree of endothelial survival. If keratoconus is to recur in a graft, one would expect some thinning associated with steepening of the graft.

In all the grafts analysed the recipient aperture and graft donor diameter were the same. The suturing was done by the continuous Perlon method to form a watertight junction, and the anterior chamber was re-established with Miochol solution (acetylcholine chloride and mannitol). This procedure, even with relaxation of the sutures and subsequent 'cheese cutting' of sutures, shows a tendency to produce a flatter than normal cornea. Analysis of the keratometry of keratoconus grafts showed that grafts steepened less than 0·2 mm of radius with an average time of 4 years from surgery (Ruben and Colebrook, 1979). This steepening may well be due to the graft taking up its normal plasticity and elasticity after removal of the sutures and thus not a keratoconus factor. The results of this report relate thickness to acuity. If a keratoconic progression is present, one would expect loss of acuity as well as the cornea to become thinner.

Patients and methods

The patients were recalled for pachometry, and the average age of the grafts was 57·6 months. The oldest graft was 10 years and the youngest 7 months from time of operation. The instrument used was the Haag-Streit pachometer attached to the slit-lamp 90 model.

Seven patients, totalling 9 grafts averaging 56·1 months after operation, were recalled for a second visit. At that visit corneal thickness was again measured but by means of an electronic pachometer based on the Haag-Streit model. The modified instrument enabled direct recording. Hence a minimum of 10 measurements were taken per eye, the mean and standard deviation being automatically calculated.

Correspondence to Mr M. Ruben.

Table 1 *Corneal grafts thickness versus cells/mm²*

Case		*Cells/mm²*	*Thickness*	*VA*
1	R	1250·83±154·04	0·558±0·014	6/6
	L	878·24±416·88	0·520±0·027	6/9
2		841·05±92·97	0·578±0·017	$6/6^{-2}$
3		1817·75±263·32	0·511±0·023	$6/6^{-2}$
4		1556·98±204·56	0·565±0·016	6/6
5		1011·29±169·60	0·540±0·008	6/6
Mean		1226·02±393·84 cells/mm²	0·545±0·026	6/6

Table 2 *Normal thickness versus cell count*

Case		*Cells/mm²*	*Thickness*	*VA*
6	R	3532·42±228·58	0·564±0·017	6/5
7	L	3029·20±176·39	0·507±0·008	6/5
8	R	3666·85±	0·571±0·026	6/5
9	R	3096·77±403·51	0·521±0·014	6/5
10	R	3288·58±49·73	0·523±0·010 mm	6/5
11		2787·87±369·10	0·527±0·018 mm	6/5
Mean		3233·62±328·38 cells/mm²	0·549±0·029	6/6

Further, the endothelial mosaic was photographed by the noncontact technique described by Zantos and Holden (1978). With our particular arrangement the initial linear magnification obtained varied between 8·9 and 20 times. Cell counting was performed on the screen of a slide-projecting system with a linear magnification of 20 times. As a control, pachometry and endothelial photography were performed on the 6 eyes of normal young adults (Tables 1 and 2).

Results

Fifty-one graft eyes were examined. The lowest reading in the 'vision line' was 0·47 mm and the thickest 0·85 mm. All eyes had measurable vision, and the average acuity with spectacles was 6/13·7. The average corneal thickness was 0·60 (Fig. 1).

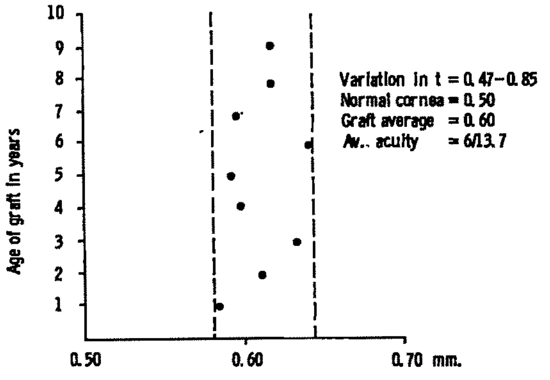

Fig. 1 *Age of graft compared with thickness*

The results for different graft age groups are as follows (Table 3):

Table 3

Age of graft	*Thickness*
Under 1 year	0·58
1	0·61
2	0·63
3	0·59
4	0·58
5	0·63
6	0·59
7	0·62
8–10	0·62

The tolerances for measurement of the corneal thickness by the Haag-Streit pachometer are ±0·02, and therefore the correlation of thickness for each age group of graft shows no significant trend (Fig. 1).

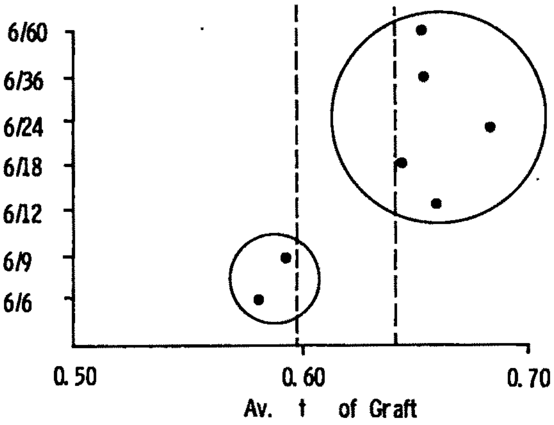

Fig. 2 *Acuity (corrected) of grafted eye compared with average thickness*

But the comparison of acuity with thickness (Fig. 2) shows the following results (Table 4):

Table 4

Acuity	*Average thickness*
6/6 or better	0·57
6/9	0·59
6/12	0·65
6/18	0·63
6/24	0·68
6/36	0·64
6/60	0·64

There appears to be a sudden significant change in thickness related to acuity when the cornea becomes thicker than 0·62 mm.

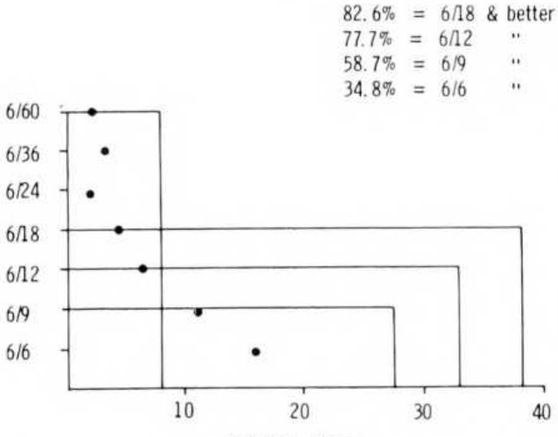

Fig. 3 *Spectacle corrected acuity distribution*

The distribution of acuity in 46 eyes where spectacle acuity was measured (Fig. 3) is as follows (Table 5):

Table 5

Acuity	*Number*				
6/6 or better	16	27	33	38 (82·6%)	100%
6/9	11				
6/12	6				
6/18	5				
6/24	2	8 (17·4%)			
6/36	3				
6/60	2				

Therefore 82·6% had distance vision of 6/18 or better with spectacles, and N5 for near with suitable addition where necessary.

The results obtained for selected corneal graft patients and normal subjects are recorded in Tables 1 and 2. All patients had normal corrected VA and there was no significant difference in corneal thickness between the mean of the 2 groups: 0·545 mm (S/D ±0·026 mm) for grafted eyes and 0·549 mm (S/D ±0·029 mm) for the control group. Endothelial cell photography on the contrary showed striking differences between the 2 groups. Cell density was lower for the corneal graft patients than for any patient of the control group: range of corneal graft densities 841 to 1817 cells/mm^2 and control group cell densities 2787 to 3666 cells/mm^2. The mean density of the control group was 2·67 times that of the corneal graft and this without any effect on corrected VA and corneal thickness.

In addition changes in cell morphology are encountered after corneal graft. Some patients showed large variations in cell sizes within the same photographic record in grafts (Fig. 4) but not in the control group (Fig. 5). In some instances there was total absence of single cells or group of cells (Fig. 6).

Conclusion

Even after 10 years in some instances and for an average of 4 years keratoconus grafts showed an increase in corneal thickness. If an upper limit of 0·54 for normal is allowed, only 15% of the grafts had thicknesses equal to or below this figure. The average thickness of 0·60 represents at least a 15% increase in thickness if normal cornea is taken to be 0·52±0·02. Therefore there is no evidence of graft cornea becoming thin or keratonic. Furthermore,

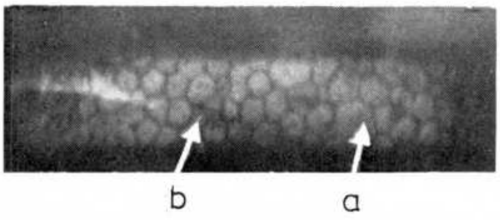

Fig. 4 *Macrophotography of endothelial cell. Corneal graft patient showing enlarged cells* (*arrow* a) *and variation in size* (*arrow* b)

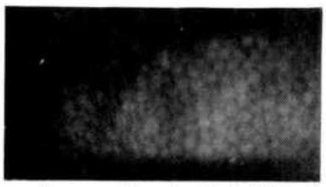

Fig. 5 *Macrophotography of endothelial cell. Normal patient*

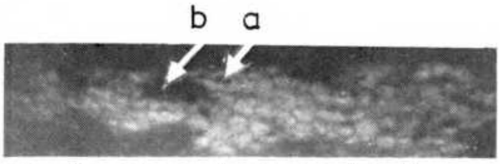

Fig. 6 *Macrophotography of endothelial cell. Corneal graft patient showing absence of cells* (*arrows* a *and* b)

when thickness was compared with the age of the graft, there was no significant variance in the thickness.

But when the acuity was compared with the thickness a relationship was obvious. It appeared that substantial loss of acuity resulted when thickness was more than 0·62. Such grafts, while clear and in some instances giving 6/6 acuity, nevertheless in many eyes are likely to be associated with subnormal acuity.

The results obtained for the endothelial study must be considered as a preliminary report, giving an indication of the changes occurring after corneal grafting and the effects they have on corneal physiology. The details of the measurement techniques will be published later. The main conclusions reached are that normal thickness is still maintained with endothelial counts a third of normal.

It remains to be proved whether those grafts associated with thicker than normal cornea had even a more diverse endothelial morphology than seen in this group. The reasons for endothelial cell death of the donor disc are several, and it is not yet determined whether cell loss is peripheral or distributed sporadically overall. Similar morphological changes occurring gradually as the graft ages have been reported by Mishima *et al.* (1979) but not with the absence of cells as seen in some of the grafts reported in this communication.

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British Journal of Ophthalmology, 1979, 63, 794–796

Gentamicin penetration and decay in the human aqueous

JEFFREY S. HILLMAN, S. I. JACOBS, A. J. GARNETT, AND M. B. KHESKANI

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SUMMARY The penetration of gentamicin into human aqueous was measured after intensive drops or subconjunctival injection of the antibiotic. The drop regimen proved ineffective in producing a therapeutically effective level. After a single 40 mg subconjunctival injection an effective concentration was achieved in 2 hours and maintained for 24 hours. The significance of these findings is discussed with respect to therapeutic implications.

Gentamicin is highly active against many of the bacteria that infect the human eye and is widely used in ophthalmology. It is particularly valuable in the immediate management of endophthalmitis where antimicrobial treatment must be instituted before bacteriological studies are completed. The antibiotic is usually administered locally as drops or by subconjunctival injection.

After the subconjunctival injection of 10 mg of gentamicin Furgiuele (1970) observed that therapeutically effective levels of the drug were attained in the aqueous of patients undergoing routine cataract extraction, and these findings were confirmed by Mathlone and Harden (1972), who used doses of 20, 40, and 80 mg. In contrast Ellerhorst *et al.* (1975) showed that 0·3% gentamicin drops failed to achieve a significant concentration in the aqueous of all of their patients except 1 even when the eye was inflamed, while MacIlwaine *et al.* (1974) found that the antibiotic failed to reach the aqueous in adequate amounts after a single intravenous dose of 1 mg/kg body weight. The clinical value of subconjunctivally injected gentamicin has been established (Goulstine and Marmion, 1971), but information is incomplete on the intraocular penetration of the drug in man and its subsequent decay in the aqueous.

The present study was undertaken to investigate the penetration of gentamicin into human aqueous from an intensive drop regimen compared with a single subconjunctival injection and to determine how long a therapeutically effective concentration would be maintained.

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Material and methods

The study was conducted on 41 eyes in 40 patients who all presented for elective cataract extraction. The age range was between 56 and 92 years, and 16 were male and 24 female. The immediate preoperative preparation consisted of cocaine and adrenaline drops for 34 eyes or cyclopentolate drops alone for 7 eyes, given 30 minutes before surgery.

In 37 eyes the antibiotic drops routinely administered preoperatively were replaced by a single subconjunctival injection of 40 mg gentamicin contained in 1 ml, given at a range of times before surgery and made into the lower fornix after surface anaesthesia with amethocaine drops. Four eyes received instead intensive treatment with 0·3% gentamicin drops timed to finish at various intervals before operation. Approximately 2·5 mg of antibiotic was instilled during this treatment which followed a regimen of 1 drop per minute for 5 minutes followed by 1 drop every 5 minutes for 30 minutes and then by 1 drop every 15 minutes for 90 minutes.

Cataract extraction was performed under an operating microscope by the ab-externo technique. A limbal-based conjunctival flap was reflected and incision made at the corneoscleral junction down to Descemet's membrane. Haemostasis was obtained and the wound dried with a compressed sponge swab to remove any antibiotic which might have been released from beneath the conjunctiva. A small incision was then made through Descemet's membrane into the anterior chamber and about 0·2 ml of aqueous aspirated via a 30 gauge anterior chamber cannula into a 1 ml tuberculin syringe, which was sealed with a cap and sent for assay. Air was allowed to reform the anterior chamber, the section

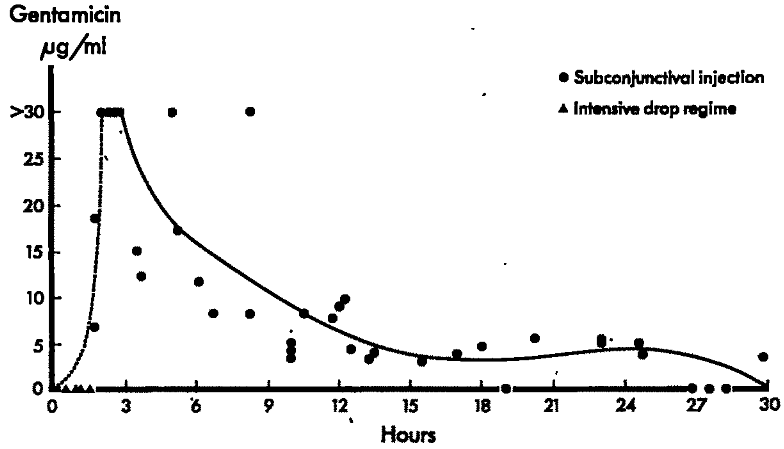

Fig. 1 *Aqueous concentration of gentamicin after its administration by 2 hour intensive 0·3% drop regimen or by 40 mg subconjunctival injection*

was completed, and cataract extraction was performed.

The microbiological assays were carried out in 10 × 10 inch (25 × 25 cm) plates by an agar diffusion method. 150 ml of antibiotic assay No. 1 agar (Mast Laboratories) seeded with a test strain of *Pseudomonas aeruginosa* donated by Nicholas Laboratories was poured into the plates, which had been levelled on an adjustable tripod. After drying, wells were cut in the plates with a No. 3 cork borer and 50 µl of aqueous dispensed by an Eppendorf pipette into each of 3 wells in a random pattern. Standards containing 2·0, 5·0, 10·0, and 20·0 µg gentamicin per ml were made up in distilled water and set up randomly in triplicate on every plate. After the application of standards and aqueous the plates were allowed to diffuse for 30 minutes at room temperature before overnight incubation at 37°C. The zones of bacterial inhibition were measured with a Luckham zone reader, and the mean diameters of the triplicate readings of the standards were plotted on semilogarithmic paper to give a straight line. The gentamicin content of the aqueous was calculated from this line extrapolated down to 1 µg/ml and up to 30 µg/ml.

Results

The results of the gentamicin bioassays are presented in Fig. 1, which relates the aqueous level of antibiotic to the time after completion of antibiotic delivery. The graph is a computer-fitted 4th degree polynomial curve obtained on a Wang 2200T computer using program f1–3–0 of Statistical General Program Library GLBR 22 A.

Drop therapy. The 4 aqueous samples taken between ½ and 1½ hours after completion of the 2-hour intensive drop regimen failed to show any detectable gentamicin. This series was then discontinued, as there was no doubt that this method of delivery had failed to approach a therapeutic level in the aqueous.

Subconjunctival injection. After subconjunctival injection of 40 mg gentamicin the aqueous concentration rose to reach very high levels in excess of 30 µg/ml after 2 hours. A high level was maintained for the first 12 hours and an adequate level for the second 12 hours after injection.

No observed differences between the gentamicin aqueous levels were attained which related to the age or sex of the patient. The postoperative clinical courses of the patients were unremarkable and there were no cases of intraocular infection.

Discussion

For an antibiotic to be effective a therapeutic concentration must be delivered to the infected tissues and maintained for an adequate period of time. The route of delivery has a great effect on the degree of penetration of a drug into the eye. When presented in drop form, absorption is thought to take place directly across the cornea. Contact time with the cornea is limited because of drainage down the lacrimonasal system, but it can be increased by increasing the frequency of drop instillation or by continuous irrigation. However, the results of the present investigation show that even after 2 hours' treatment with frequent 0·3% gentamicin drops little antibiotic reaches the aqueous in the noninflamed eye. If therapeutically effective aqueous levels of gentamicin are required, as in the management of endophthalmitis, topical drop delivery alone is inadequate.

The poor penetration obtained with topical drop therapy contrasts with the efficacy of subconjunctival injection in achieving high aqueous levels. The figure shows that concentrations of more than 4 μg/ml aqueous are attained within 1–2 hours of a single 40 mg subconjunctival injection and that by 2–3 hours very high levels of the antibiotic, in excess of 30 μg/ml, are present in the anterior chamber. The concentration of gentamicin falls over the first 12 hours to reach a level of about 4 μg/ml, which is maintained for the next 12 hours.

In the treatment of infective endophthalmitis a high concentration of antibiotic in the anterior chamber is essential, and a level of 4 μg/ml is likely to be bactericidal for all the commonly encountered aerobic and facultatively anaerobic pathogenic bacteria except the streptococci (Garrod *et al.*, 1973). Obligate anaerobes are highly resistant to gentamicin, but streptococci, which are moderately resistant to gentamicin alone, frequently show a synergistic response to a combination of gentamicin and a penicillin (Watanakunakorn, 1971). A concentration of 4 μg gentamicin per ml in the aqueous represents the minimum inhibitory concentration of the drug for *Ps. aeruginosa*, which is refractory to many other antibiotics and a cause of grave endophthalmitis. The published values for the minimum inhibitory concentration of gentamicin for this organism vary widely because the results obtained are dependent on the magnesium content of the medium used in the test system (Garrod and Waterworth, 1969). As the magnesium ion concentration of the aqueous is approximately 80% of that found in plasma, it seems prudent to accept the high value of 4 μg gentamicin per ml as the minimum effective level in the aqueous for *Ps. aeruginosa* infections.

Although the present observations show the likely therapeutic value of a subconjunctival injection of 40 mg gentamicin, the design of the study did not allow the direct evaluation of the possibility of antibiotic accumulation in the aqueous after repeated injections, but prima facie this seems unlikely. Twenty-seven hours after a subconjunctival injection gentamicin was not detectable in the aqueous in 3 cases. In clinical practice a limiting factor for repeated subconjunctival injections is the clinical state of the conjunctiva, which may become indurated. If this occurs, injections may be given into a deeper plane, as experiments in the monkey by Barza *et al.* (1978) have shown penetration with good posterior segment levels and smaller anterior segment levels on retrobulbar injection of gentamicin.

A theoretical risk from repeated subconjunctival injections of gentamicin in patients with impaired renal function is the possibility of systemic accumulation of the drug with risk of toxicity. It is most unlikely that a single 40 mg injection of gentamicin would prove hazardous in a patient of average build even with poor renal capacity, but, if injections are frequent or renal function impaired, the serum level of the antibiotic should be monitored and therapy modified accordingly.

We thank Mr F. T. de Dombal for statistical advice and the Department of Medical Illustration at St James's University Hospital for the preparation of the Figure.

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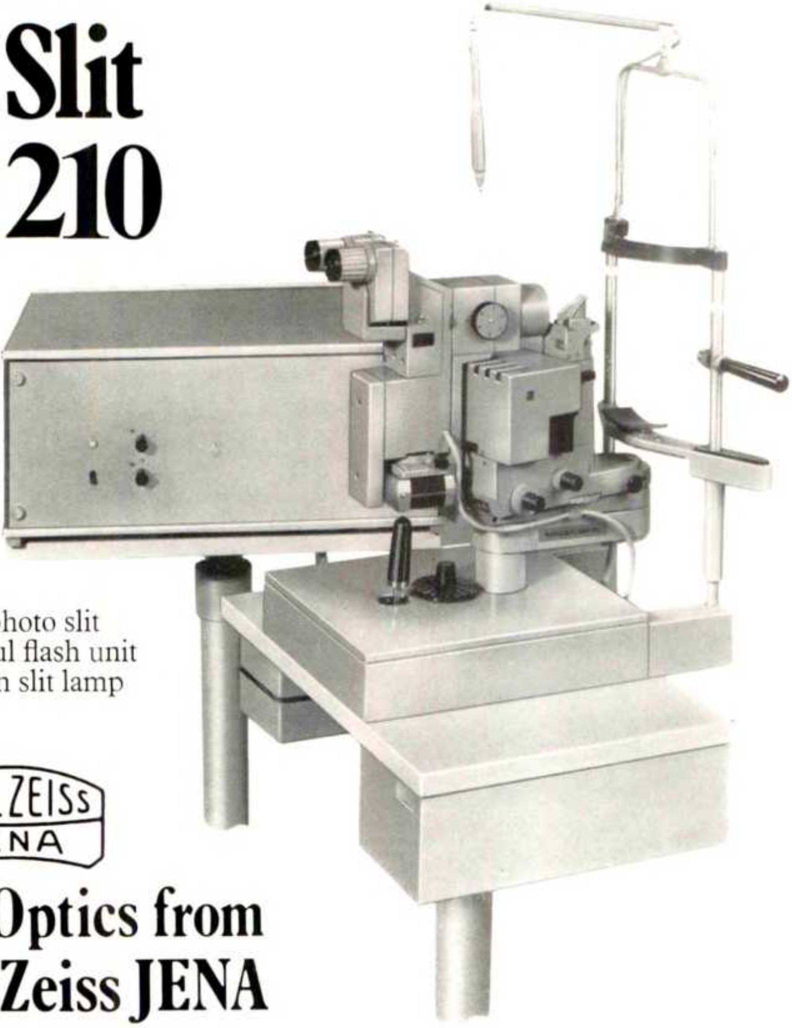

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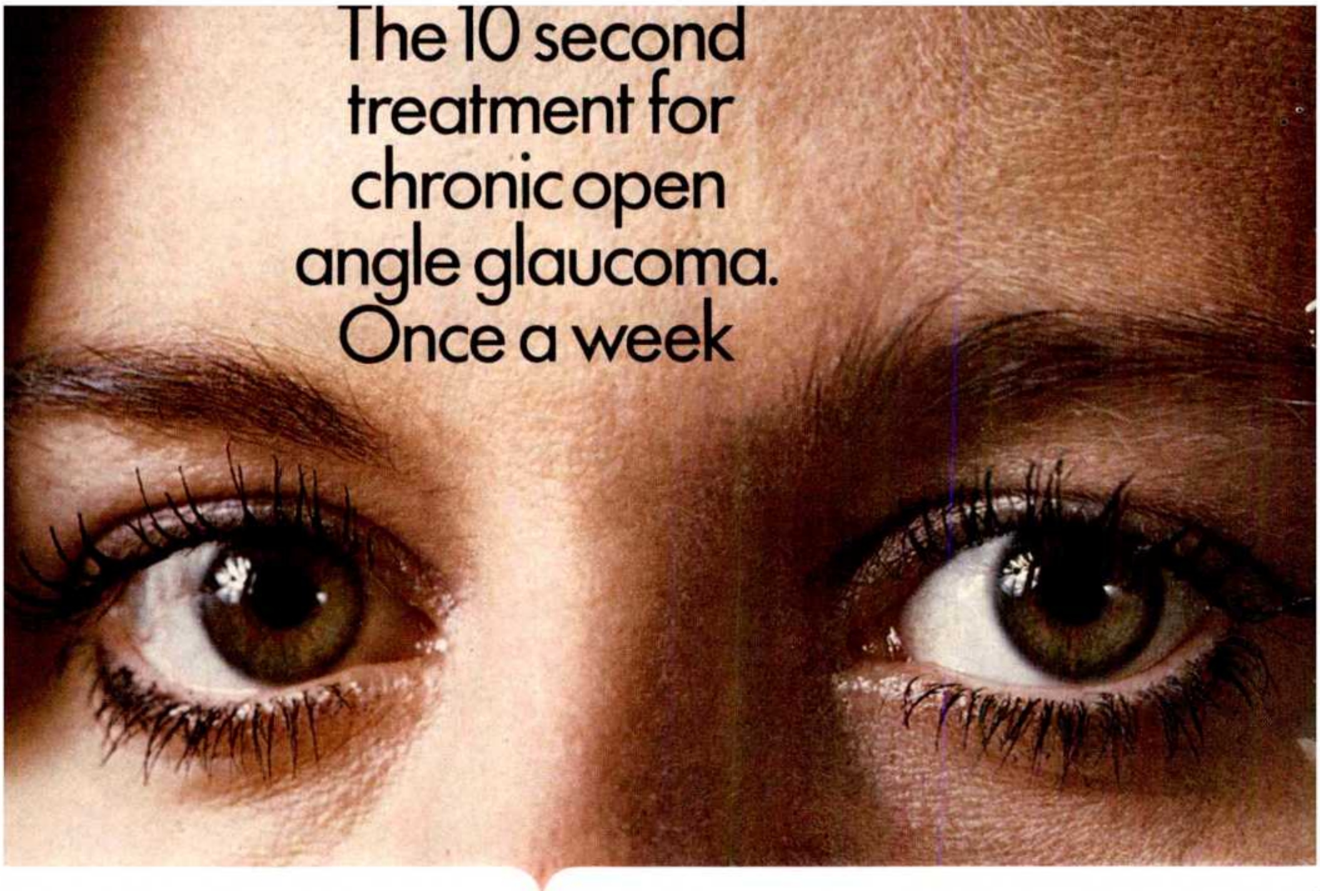

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Book reviews

Parsons' Diseases of the Eye. 16th edn. By STEPHEN J. H. MILLER. 1978. Pp. 598, figs. Churchill Livingstone, Edinburgh (£10)

The sixteenth edition of 'Parsons' appears with a new editor, only the third in this classic textbook's 70 years' history. This book has the distinction and indeed the responsibility of being the basic annual of instruction of many thousands of ophthalmologists, and the whole gamut of ophthalmology is covered in some 600 pages of very concisely written text.

It is not difficult to discover the editor's special interests, for the chapters on neuro-ophthalmology, glaucoma, and ocular motility have not been bettered in far larger textbooks. This edition is particularly well balanced, so that a beginner in ophthalmology would find nearly every aspect covered. The descriptions of some techniques, as for example on the theory and practice of photocoagulation and fluorescein angiography, might well be expanded in the next edition, and some of the black-and-white photographs of pathological conditions in the anterior segment could be better shown by drawings.

In general, however, this is an excellent textbook and a worthy successor to the previous editions. It is remarkable that it has been possible to compress so much information in a single volume, and it should attract a particularly wide readership.

J. H. DOBREE

Glaucoma, Conceptions of a Disease: Pathogenesis, Diagnosis, Therapy. Ed. KLAUSE HEILMANN AND KENNETH T. RICHARDSON. Pp. 434. £35·00. Holt-Saunders: Eastbourne. 1978.

The editors of this very readable and worthwhile book have started from the premise that 'the "disease" glaucoma—although defined as an interrelationship between elevated intraocular pressure, visual field loss and optic nerve disease—is not the same thing to all men—at least to all glaucoma experts.' The editors have selected a number of acknowledged authorities on glaucoma and asked from each an outline of their ideas on the disease, 'with information on the present state and continuing development of glaucoma research'. The authorities chosen have rewarded us with discussions on their chosen field within glaucoma. The editors have combined these discussions into sections, each discussion comprising a chapter or part of a chapter within a section. The result is a book for the clinician which has special emphasis on basic sciences and also a book for the basic scientist needing readable chapters on clinical glaucoma. Most chapters are extensively referenced, allowing easy progression to original papers for any point in the text that the reader may wish to explore in greater detail.

The book may be divided into 2 unequal parts. The first, containing sections on 'conceptions', basic sciences, pathogenesis of glaucoma damage, methods of examination and pharmacology, accounts for the first 300 pages, while the last quarter of the book deals with 'management', 'surgical techniques' and 'classification and synthesis' in that order. The book is introduced with a foreword by Hans Goldmann and has an epilogue by Stephen Drance.

Despite the authors' original introduction of individualistic ideas about glaucoma there is remarkably little dissent between authors within the book. In an excellent chapter on the chamber angle Rohen states that intraocular pressure does not increase with age—a point at variance with the conclusion reached by Worthen 2 chapters later. Rohen observes age related changes in the trabecular meshwork, and, noting that the outflow facility falls with age while intraocular pressure apparently does not, considers that aqueous production must also fall. This may well be true, but not necessarily for the reason stated.

Henkind explains glaucomatous visual field defects on the basis of loss of the radial peripapillary capillaries in one chapter, only to have this explanation attacked and near demolished by Hayreh in the succeeding chapter. Hayreh, in 2 comprehensive chapters, describes the structure of the optic nerve and the pathogenesis of visual field defects. He summarises his own work and critically reviews others' work in this field before concluding that visual field defects in glaucoma *must* be vasogenic in origin. While his conclusions are not universally accepted, none can disagree with the volume and quality of work Hayreh has carried out while investigating this problem.

Apart from slight disagreements between authors the reader has been given many excellent chapters, frequently containing useful tips to assist us in the management of patients with glaucoma. Although it is not possible to mention each, a few will be commented on here.

The section entitled 'Glaucoma damage' includes a discussion by several authors on visual field loss. An important contribution by Aulhorn describes the earliest visual field defects detected in glaucoma patients at Tübingen, while Heilmann discusses progression and regression of visual field defects. Under the section 'Methods of examination' an excellent chapter by Greve discusses different methods of perimetry, concentrating on static perimetry. One point which these authors might have discussed more fully when describing very, very early defects is their reproductibility, for identification of such defects by static perimetry is of little use if the defects reflect only transient aberrations in the receptor system.

'Methods of examination' concludes with a practical treatise on photography by Reidel, put in perspective by the editors in a discussion entitled 'Clinical value of photography', in which they separate photography for record purposes from photography to document progression of the disease. The editors stress the limitations and value of colour photography of the optic discs in this latter regard.

Richardson, in discussing 'Management', emphasises the role of 'office phasing' and describes a therapeutic trial that should be undertaken before embarking on long-term topical glaucoma therapy. He divides the patients with chronic open-angle glaucoma into degrees of 'functional status' and manages them accordingly

Kolker identifies problems in management of glaucoma patients with interrelated diseases, stressing the potential role of systemic hypotensives in reducing optic nerve perfusion. He notes that, while beta blocking agents lower both systemic and ocular pressure, other systemic hypotensives may significantly reduce perfusion pressure at the optic nerve by leaving intraocular pressure unchanged. Clonidine is particularly singled out because the ocular hypotension is considered by some to follow ocular vasoconstriction—not an ideal state for the glaucomatous optic nerve. Kolker also emphasises the role of the ophthalmologist in informing the patient's physician of the existence of asymptomatic shallow anterior chambers, for such a patient might be considered at risk should systemic drugs that produce mydriasis be prescribed.

In the section on management Krupen and Podos adopt an almost didactic approach when classifying the primary glaucomas together with identification of symptoms and signs. Of particular importance are their paragraphs entitled 'problems for consideration', in which they outline imperfectly resolved questions that affect both closed- and open-angle glaucomas. These 2 authors have written a masterly account of the primary glaucomas; it should be on the reading list of all Fellowship candidates.

The book contains a wide range of subjects, written by acknowledged experts in Europe and the USA. Despite expected divergences of opinion it possesses as a whole a remarkable cohesiveness, for which the editors are to be congratulated. The book is a worthy addition to any ophthalmologist's library and should act as a useful reference source for many of the problems met with in dealing with glaucoma patients. ROGER HITCHINGS

Plasties et reconstructions orbito-palpébrales. By DENYS MONTANDON and GASTON F. MAILLARD. Pp. 128. SwFr 75·00. Médecine et Hygiène: Geneva. 1979.

This book on plastic surgical techniques in the orbital region is written in French, but the excellent line diagrams next to operative photographs illustrate the procedures so well that only a minimal understanding of the language is necessary. It is well researched with a short historical introduction and an excellent bibliography at the end of each chapter. Basic techniques are covered at the beginning of the book and the text is subsequently kept to a minimum. The section on eyelid reconstruction is especially well presented and reflects the author's excellent training in plastic surgery. It provides a very good appreciation of what soft tissue reconstructive procedures are available in this region. By contrast ptosis surgery and the correction of eyelid malpositions are not adequately covered for an ophthalmologist, although references for further reading are given in the bibliography. Fractures and orbital skeletal surgery for congenital malformations are discussed, but the correction of soft tissue anophthalmic socket deformities and lacrimal disorders are considered too briefly for an ophthalmologist. It is therefore primarily a book for plastic surgeons operating in the orbital region, but it should also be of use to ophthalmologists, particularly those prepared to embark on more extensive and ambitious eyelid reconstructions. J. R. O. COLLIN

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In addition to the existing awards the trustees have decided to create an additional travelling fellowship of up to £2000 in any one year which would involve the applicant attending one centre for a continuous period of not less than 6 months. Applications are now invited from consultant ophthalmologists or senior registrars in the United Kingdom about to take up consultant appointments, and any other suitable applicants, the latest date for receipt of such applications to be 31 March 1980, which will be considered by the trustees in July 1980. Further information from the Secretary, Keeler Award, Angus, Campbell & Co., Metropolis House, 39/45 Tottenham Court Road, London W1P 0JL.

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In accordance with the Vancouver agreement many medical journals are to standardise the instructions they issue to authors on the preparation of articles. References will be cited by the numerical system already familiar in many journals, including the *British Medical Journal*.

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1 Green A B, Brown C D, Grey E F. A new method of measuring the blood glucose. *Br J Ophthalmol* 1980; 64:27-32.

2 Green A B, Brown C D. *Textbook of Medicine.* London: Silver Books, 1980.

3 Grey E F. Diseases of the pancreas. In: Green A B, Brown C D, eds. *Textbook of Medicine.* London: Silver Books, 1980; 349-362.

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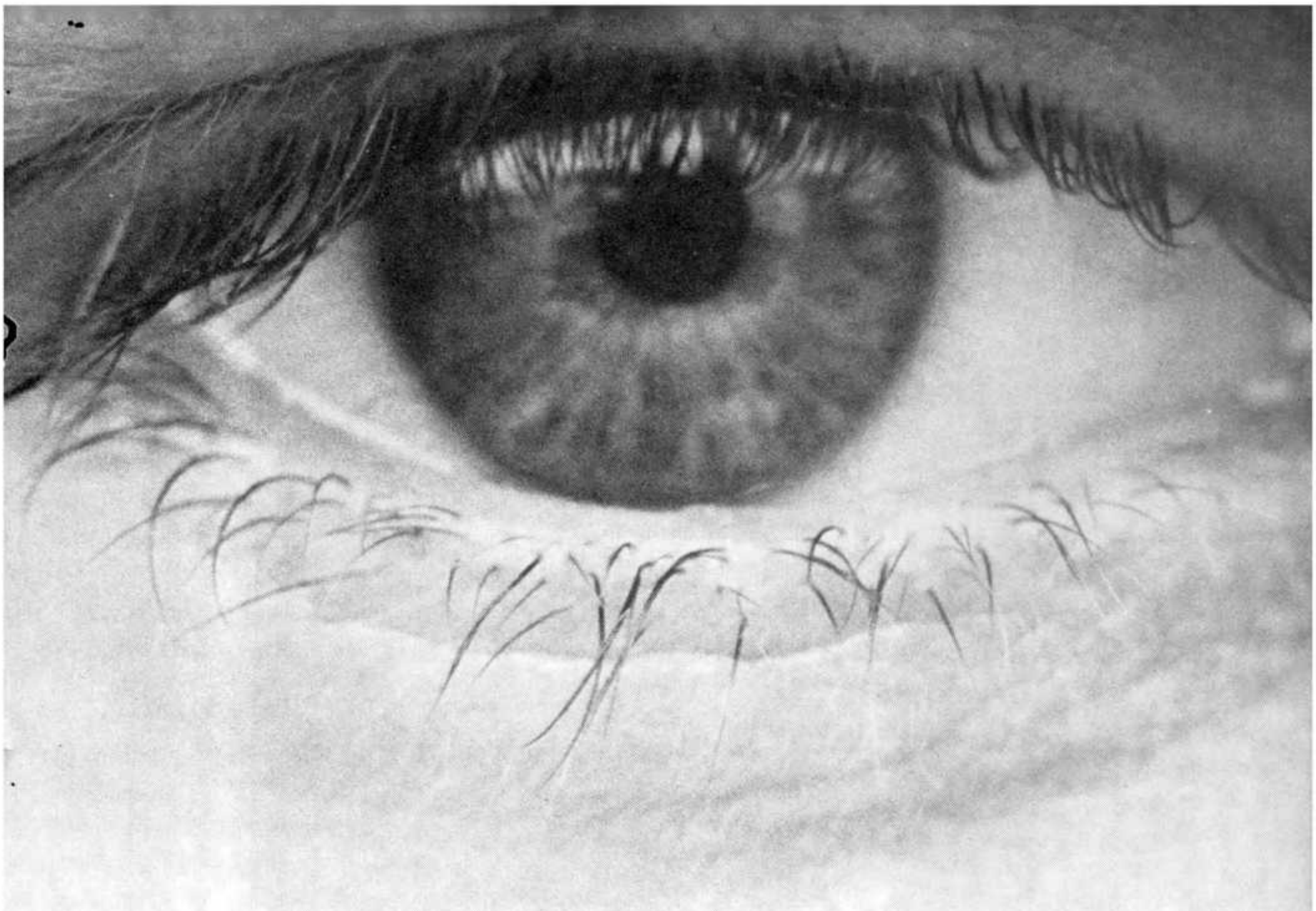

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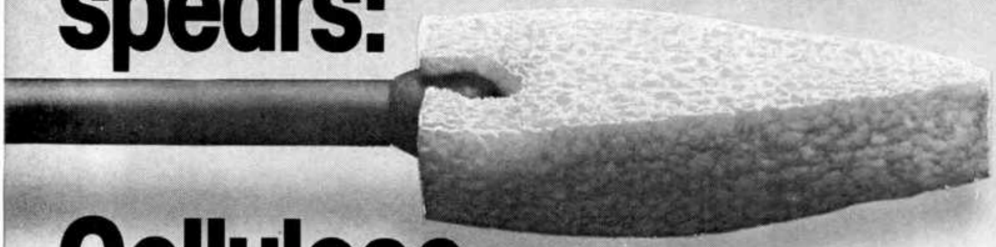

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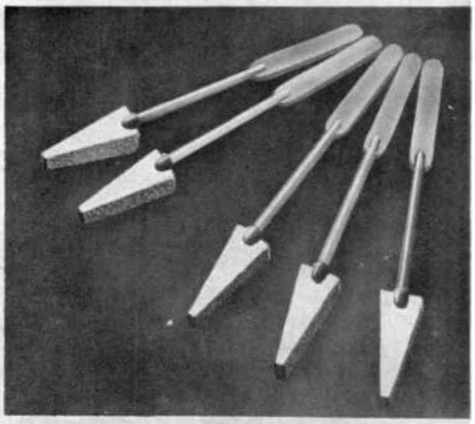

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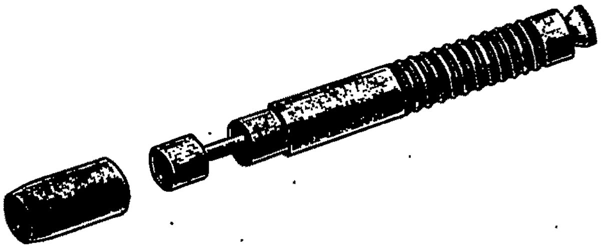

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The main theme of the Congress will be the Ergophthalmology of transport, including air, sea and land transport, and visual requirements in the home. The official language of the course will be English.

Free papers are invited in English, but priority will be given to those relating to the main theme. Titles of papers together with a short summary, not exceeding 300 words, should reach the secretary as soon as possible, preferably by January 1st.

Congress fee will be £50, including light refreshments, lunch on Saturday 19th April, and official reception on Saturday evening.

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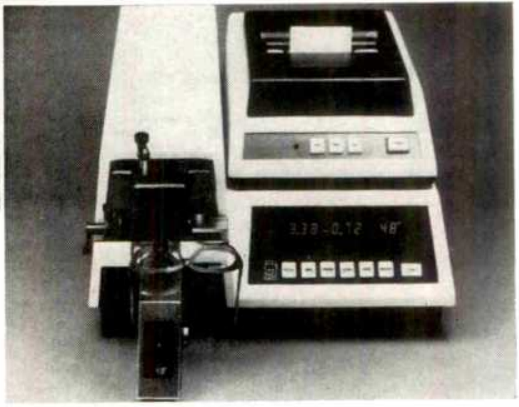

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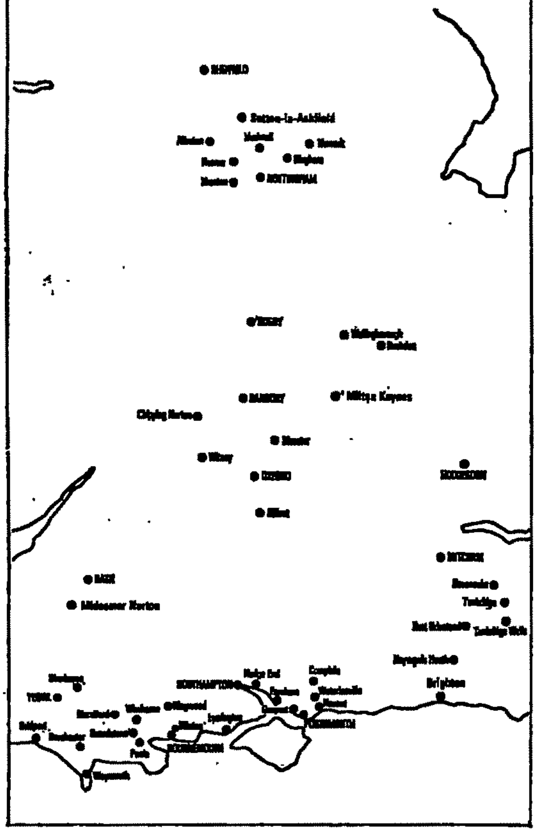

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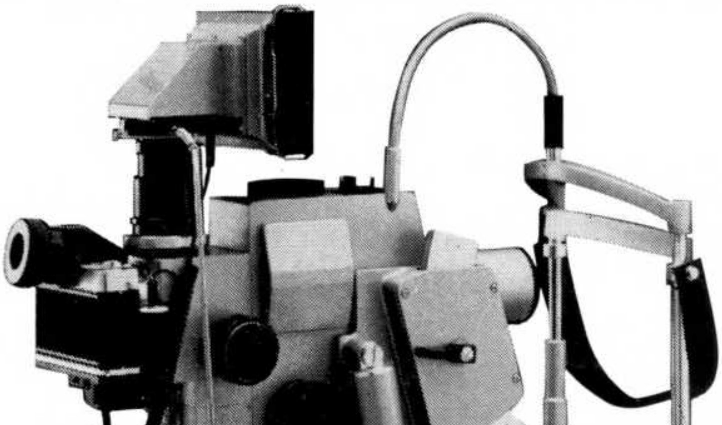

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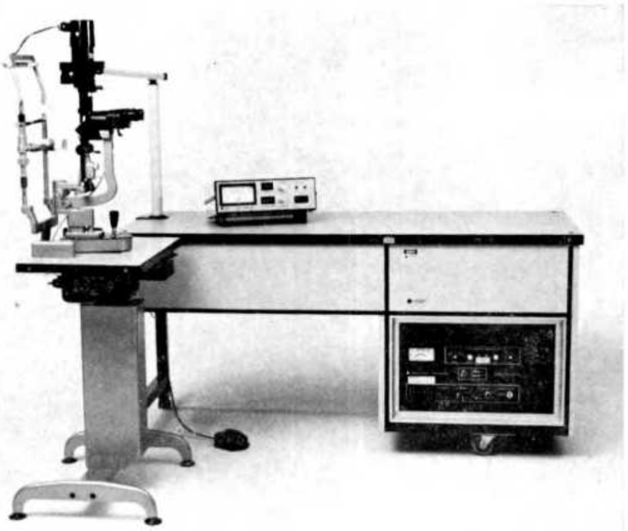

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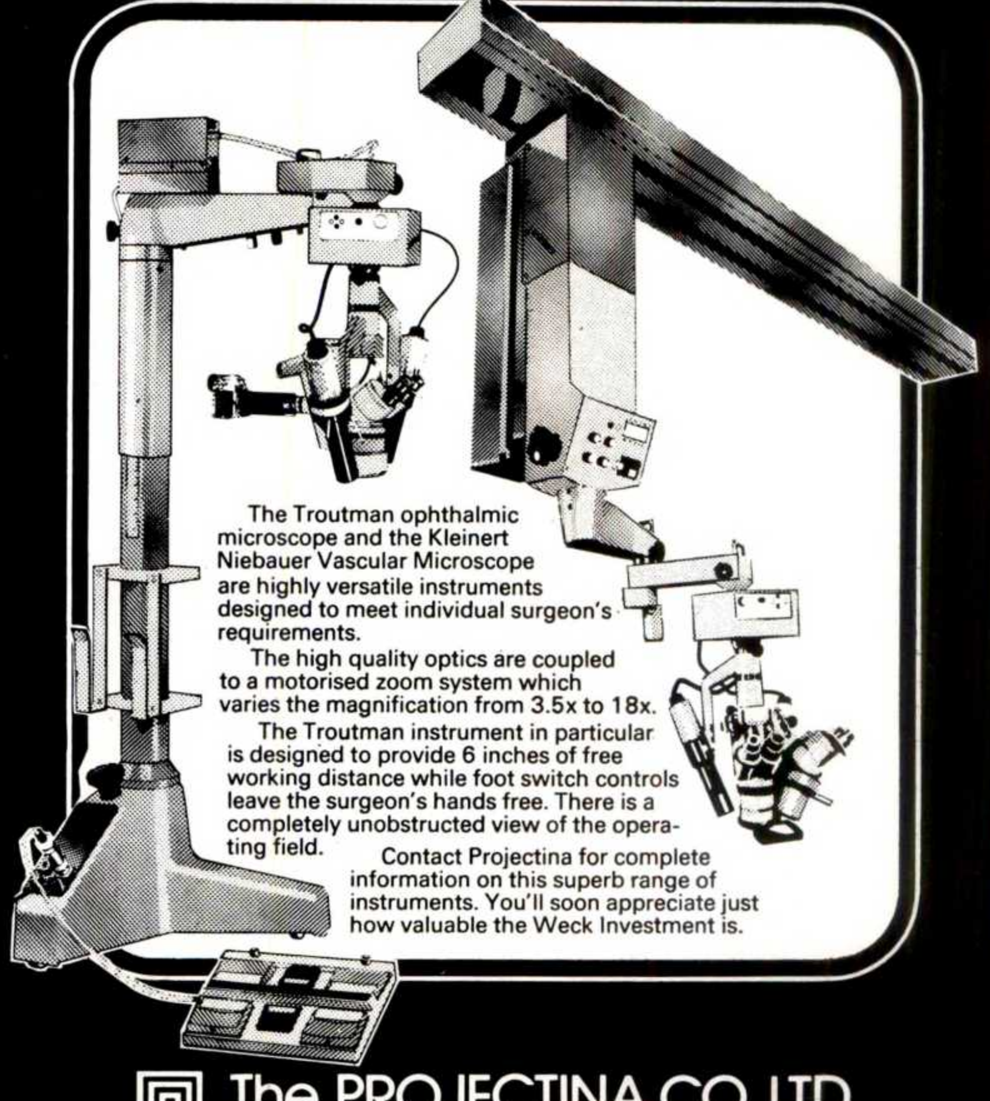

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British Journal of Ophthalmology, 1979, **63**, 799–804

Continual monitoring of intraocular pressure: effect of central venous pressure, respiration, and eye movements on continual recordings of intraocular pressure in the rabbit, dog, and man

R. L. COOPER, D. G. BEALE, I. J. CONSTABLE, AND G. C. GROSE

From the Department of Ophthalmology, University Department of Surgery,
University of Western Australia

SUMMARY A new method has been devised for continual monitoring of intraocular pressure by radiotelemetry. The use of this instrument for monitoring intraocular pressure in a variety of ophthalmic conditions is described.

Diurnal variation in intraocular pressure (IOP) has been recognised for many years. A practical method for noninvasive monitoring of IOP would be important for the diagnosis and management of several forms of glaucoma, particularly the low tension group (Phelps *et al.*, 1974). Intraoperative and postoperative monitoring may be useful for early warning of acute IOP elevation. Such a system will also provide valuable information on the effects of normal physiological processes on intraocular pressure.

Previous attempts at developing such systems have been reviewed elsewhere (Cooper *et al.*, 1979a). In this laboratory we have developed a method of noninvasive passive radiotelemetry of IOP. This communication reports the development of the system up to the present and illustrates its use in conditions designed to simulate clinical situations.

Materials and methods

Previously described miniature guard ring applanating transensors (AT) (Cooper and Beale, 1977) were mounted in acrylic or Sauflon haptic elements individually designed for the human, rabbit, or dog. The human AT holder was modelled from a standard acrylic haptic whose central optic was removed. The AT was mounted in the lower part of the scleral haptic so that it applanated the inferior sclera under the lower lid. The whole haptic ring was placed in the conjunctival fornix (Fig. 1). The rabbit and dog ATs were mounted in simple bilobed haptics, which rested in the upper conjunctival fornix of the rabbit or were sutured to the sclera in the dog eye.

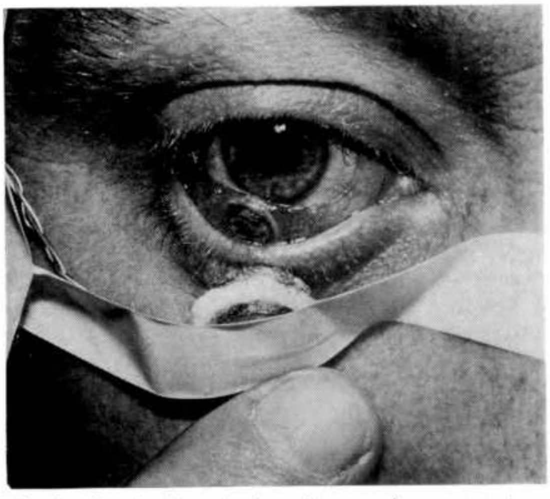

Fig. 1 *Continual monitoring of intraocular pressure in man. The lower lid, to which is attached the ACFM aerial, has been everted to show the underlying transensor embedded in an acrylic haptic*

Intraocular pressure was monitored with an automatic continual frequency monitor (ACFM) invented by one of us (DGB). This miniaturised monitor was fixed to the head by elastic bands.

Correspondence to Dr R. L. Cooper, Department of Ophthalmology, University of Western Australia, Royal Perth Hospital, Box X 2213, GPO, Perth, Western Australia 6001.

The aerial was glued to the surface of the lower lid, overlying the AT, with silicone rubber adhesive (Dow Corning) (Fig. 1). The ACFM induces electromagnetic oscillations in the AT. The frequency of the oscillation is varied continually over the range of the resonant frequencies of the AT. The resonant frequency (Rf) of the AT is directly proportional to IOP. The ACFM monitors these changes in Rf and transmits the resonant frequency to a remote radio receiver, whose output is converted to an analogue signal recorded on a standard single channel chart recorder or processed by a Hewlett-Packard 9825 A computer and subsequently recorded on a 4-channel plotter (HP 9872 A). The tracing obtained is thus in the form of a continual variation of Rf, expressed in kilohertz (kHz), which faithfully follows IOP fluctuations.

Recordings of IOP were made in the anaesthetised dog and rabbit and in one conscious person.

GENERAL ANAESTHESIA

The effects of suxamethonium, the Valsalva manoeuvre, and Pco$_2$ variations on IOP were studied in the anaesthetised dog. The dog was intubated and maintained either under spontaneous respiration or intermittent positive pressure ventilation (IPPV). Central venous pressure (CVP) was recorded in this animal with a Sanborn pressure transducer.

In the rabbits IOP recordings were made with the animals maintained by intermittent intravenous injection of pentobarbitone sodium into an ear vein. Studies were made of the ability of the monitor to follow rapid variations in IOP due to pulse, respiration, and variations in depth of anaesthesia. Depth of anaesthesia was monitored by the lash reflex. The effect of digital pressure on the eye was recorded in this animal.

THE CONSCIOUS HUMAN

In man transducer stability and ability to follow rapid changes in eye IOP with respiration, eye movements, and lid closure were investigated. The response of the monitor was tested against intermittent recordings of IOP with a Mackay-Marg tonometer (Berkeley Electronics).

Results

IOP MONITORING UNDER ANAESTHESIA

The Valsalva manoeuvre was simulated by manual compression of the canine chest during the inhalation stroke of the ventilator. This resulted in a small rise in IOP (Fig. 2). Mean CVP was shown to rise from the initial level of zero to mean pressure of 10 mmHg (Fig. 3).

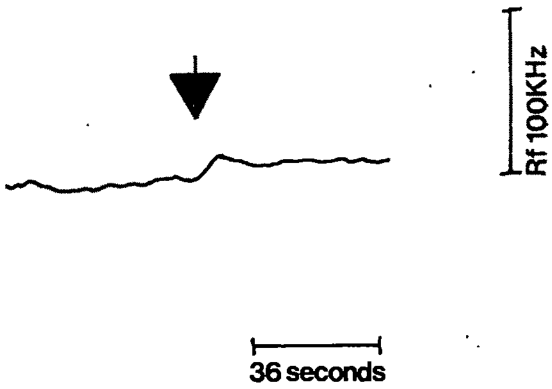

Fig. 2 *Continual monitoring of IOP in the dog under anaesthesia. Tracing of IOP record; the arrow indicates the time of compression of the chest in a simulated Valsalva manoeuvre, which resulted in a small rise in IOP*

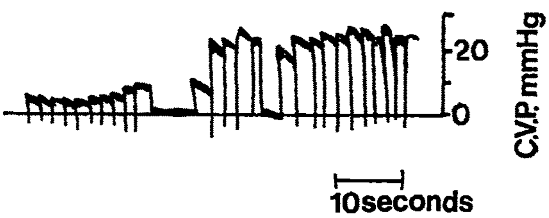

Fig. 3 *Trace of central venous pressure recorded by a Sanborn pressure transducer in the anaesthetised dog. The Valsalva manoeuvre was simulated by manual compression of the thorax: mean CVP rose from 0 mmHg to 10 mmHg. This recording was made simultaneously with that of Fig. 2*

Injection of suxamethonium intravenously in the dog caused a dramatic rise in IOP, which lasted approximately 40 seconds, and settled to a level below baseline. The level to which IOP rose was more than 30 mmHg, however, as can be seen from the tracing; the range of the recorder was not high enough to record the maximum peak of IOP (Fig. 4). The CVP recording showed a similar rise in mean venous pressure from zero to approximately 15 mmHg, with a gradual decline to a mean CVP of approximately 5 mmHg (Fig. 5).

Variations in Pco$_2$ were accompanied by minimal changes in IOP. Correlation between Pco$_2$ and IOP was poor, whereas correlation between IOP and pH was better.

In the rabbit recordings of IOP showed high frequency excursions of IOP which were synchronous with the pulse. Well-defined low-frequency excursions of IOP due to respiration were observed

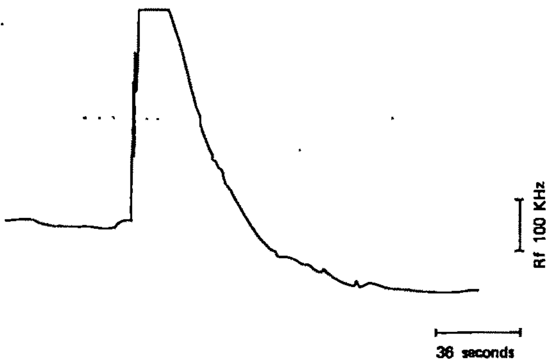

Fig. 4 *Continual recording of IOP in the anaesthetised dog by radiotelemetry. The trace shows a sudden rise in IOP due to intravenous suxamethonium injection. IOP falls below baseline as relaxation occurs*

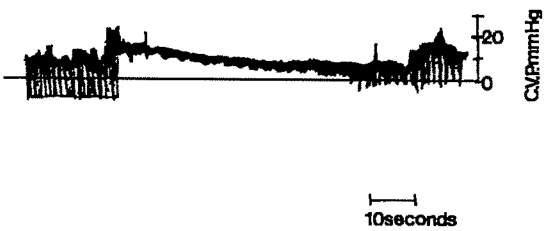

Fig. 5 *The effect of suxamethonium on central venous pressure recorded by a Sanborn pressure transducer in the anaesthetised dog. Mean CVP rose from 0 mmHg to about 12 mmHg. Recording was made simultaneously with that of Fig. 4*

in all recordings. An example of such a recording is shown in Fig. 6.

If the depth of anaesthesia in the rabbit was allowed to decrease, there was invariably a rapid rise in intraocular pressure, as the rabbit regained lash reflex, and tone of eyelids and extraocular muscles. An example of a sudden rise in the pressure is shown in Fig. 7. The rapid excursions are due to respiration. With further injection of pentobarbitone and loss of lash reflex the IOP fell to approximately 10 mmHg. During the period of lightened anaesthesia the rabbits developed eye rolling movements and eventually blepharospasm, due to the presence of the haptic.

The effect of digital pressure through the eyelids in the rabbit is dramatically shown in Fig. 8. High spikes in intraocular pressure are seen towards the end of the recording, which were due to the application of a Mackay-Marg tonometer in order to correlate the monitor output with applanation pressures. The IOP fell to just below baseline following this pressure on the eye.

MONITORING OF IOP IN THE CONSCIOUS HUMAN

Recording of the effect of heartbeat and respiration is shown in Fig. 9. As in the rabbit recordings, a high-frequency ripple is superimposed on the main recording, which was synchronous with pulse. The lower frequency variation was due to respiration. The effect of forced inspiration and expiration on IOP is shown in Fig. 10. Inspiration is accompanied by a rapid fall in IOP, with the converse occurring

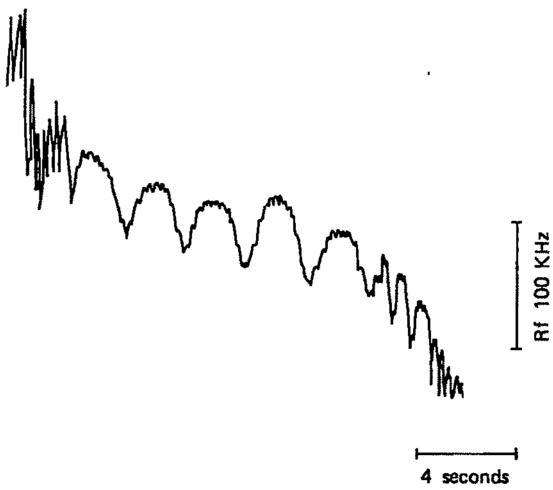

Fig. 6 *Continual recording of IOP in the anaesthetised rabbit by radiotelemetry. The ripple is due to pulse and low-frequency variations to respiration*

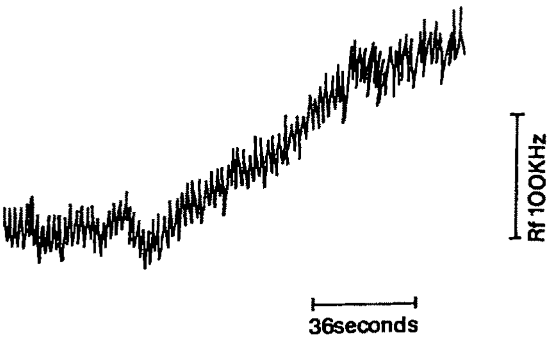

Fig. 7 *Response of IOP to lightening of depth of anaesthesia in the rabbit. Blepharospasm and contraction of extraocular muscles cause a rise in IOP lasting about 2 minutes; rapid variations in IOP are due to respiration*

on expiration. The effect of heartbeat is well shown. Inspiration and breath holding cause an initial reduction in intraocular pressure, followed by a gradual rise as the glottis is closed off (Fig. 11). During this manoeuvre there was always shown to be a short rise in IOP prior to the glottis being closed off and the chest wall relaxing.

Maximal gaze from right to left was accompanied by a rise and fall of IOP. In Fig. 12 the response of

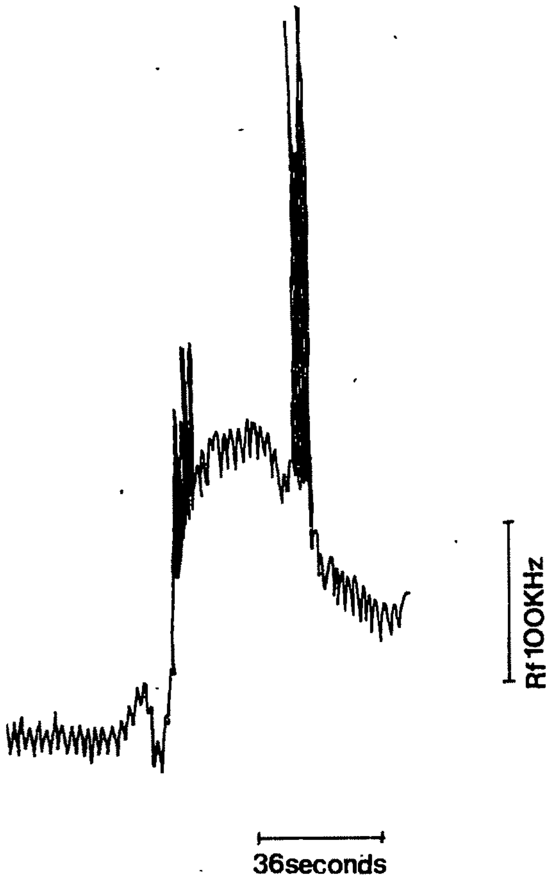

Fig. 8 *Ocular hypertension induced by digital compression of the eye of the anaesthetised rabbit. The high spikes are due to intermittent Mackay-Marg tonometry*

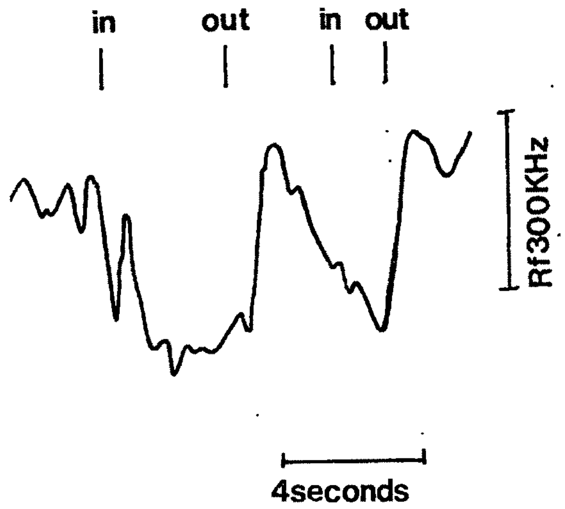

Fig. 10 *Continual recording of IOP in the conscious human: the effect of deep breathing on IOP. In=respiration, out=expiration. Deep inspiration (in) decreases resonant frequency by approximately 270 kHz. Expiration (out) causes a rise of approximately 300 kHz. The rise and fall in IOP cannot be accurately estimated in mmHg without extensive calibration studies*

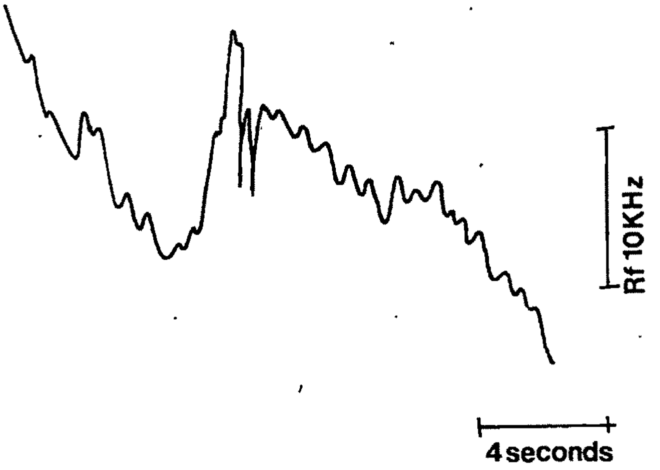

Fig. 9 *Continual recording of IOP by radiotelemetry in the conscious human. Note the excursions due to pulse and respiration*

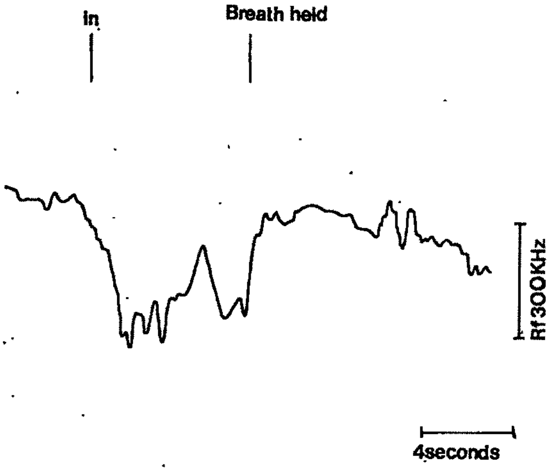

Fig. 11 *The effect of breathholding in the conscious human. IOP decreases on inspiration, and increases to baseline on closure of the glottis.*

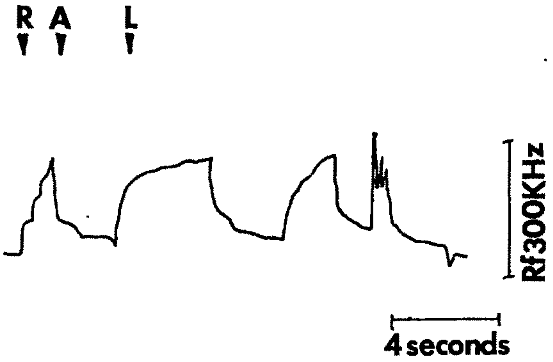

Fig. 12 *The effect of maximal eye movements on IOP in the human: R=right gaze, A=primary position, L=left gaze. Subsequent changes in IOP are due to similar alternating gaze movements ending in a rapid movement to the left, reverting finally to the primary position. True change in IOP cannot be accurately assessed in mmHg. Some of the rise in IOP may be due to distortion of the sclera by the acrylic haptic*

the IOP monitor to right gaze (R) return to the primary position (A) and then full left gaze (L) followed by a repeat of the manoeuvre is shown. These IOP variations are about 10 mmHg.

Blepharospasm is thought to cause a rise in intraocular pressure, which was demonstrated in the rabbit experiments. In man closure of the eyelids resulted in a sustained rise in intraocular pressure (Fig. 13). The IOP rose approximately 7 mmHg in this experiment. It will be noted at the beginning of this recording that there are multiple high spikes in the IOP recording. These are blink artefacts, the amplitude of which do not fully reflect IOP, but are due to rapid variations in inductive coupling between the AT and the aerial, as shown by oscilloscopic monitoring.

The response of the monitor to IOP, when tested against intermittent recordings with the Mackay-Marg tonometer, correlated well with the tonometry readings for up to 2 hours of continual recording. There was then a decline in Rf. We were interested in the effect of continual application of the Mackay-Marg tonometer to the cornea for purposes of calibration of the instrument for individual eyes. The results of these experiments are reported elsewhere (Cooper *et al.*, 1979b). Fig. 14 illustrates the Mackay-Marg tracing above and the monitor output below. The monitor output faithfully reproduces the rise in IOP induced by the tonometer application. The superimposed fluctuations due to heartbeat, respiration, and tremor of the hand holding the tonometer are reproduced in both tracings.

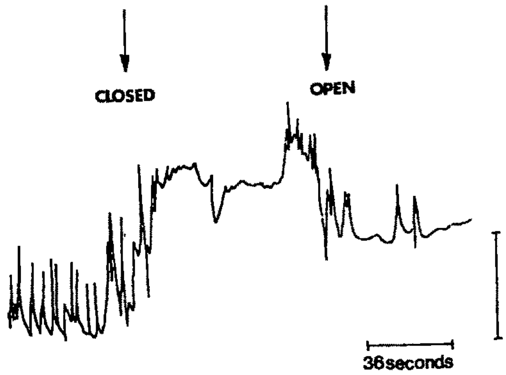

Fig. 13 *Continual recording of IOP in the conscious human by radiotelemetry. Closure of the eyelids causes a rise in IOP. The rapid spikes are blink artefacts (see text)*

Discussion

It is well known that IOP is normally maintained at a constant level with only minor diurnal variations. There is some compensation for rapid variations of IOP by the viscoelastic properties of the globe and by eflux of blood from the choroid. However, rapid rises of IOP cannot be fully accommodated by either mechanism. We simulated several conditions that are known to cause acute ocular hypertension during eye surgery. We have demonstrated 2 mechanisms for suxamethonium induced ocular hypertension, namely, contraction

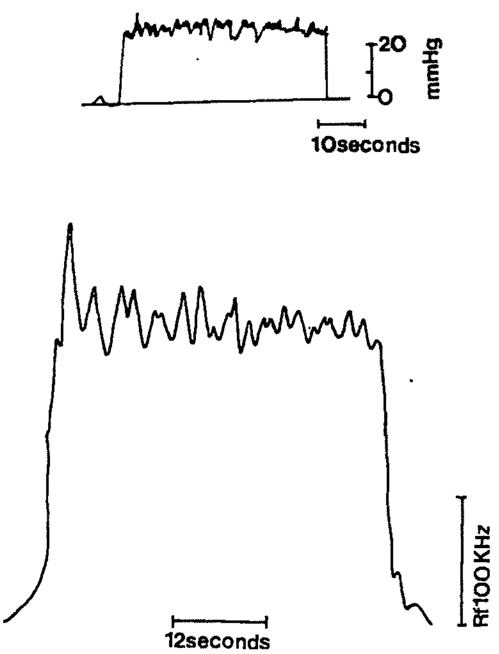

Fig. 14 *The effect of continual Mackay-Marg tonometry on IOP in the anaesthetised dog. The upper tracing was obtained from the Mackay-Marg tonometer held on the cornea and the lower tracing from the IOP monitor. The tracings were obtained simultaneously but with different amplitude and time scales. The peaks and troughs recorded by each instrument can be correlated in order to arrive at a calibration of the monitor. These small variations in IOP are due to pulse, respiration, and small movements of the Mackay-Marg tonometer on the cornea. Note the superior sensitivity of the passive telemetric monitor compared to the Mackay-Marg tonometer.*

of orbital muscles and a rise in mean CVP. This confirms observations of previous workers (Lincoff *et al.*, 1955; Adams & Barnett, 1966). We were also able to demonstrate the effect of increasing tone in orbital muscles with lightening of anaesthesia.

In the conscious human we recorded the effects of voluntary eye movements, lid closure, and respiratory excursions. The results thus show that our monitor is capable at least of rapid response and semiquantitative assessment of intraocular pressure over 2 hours.

Despite the capabilities of our system to record noninvasively, several problems remain to be resolved. Individual variations of the scleral rigidity and variation of rigidity with IOP mean that thorough calibration studies will have to be conducted in man with this type of pressure transducer.

The materials from which the AT is constructed have to be improved in order to reduce water vapour permeability for long-term stability. Mechanical problems with the AT and its coupling to the sclera have to be overcome in order to improve accuracy enough to make the instrument capable of quantitative assessment of IOP over at least 24 hours.

The final system, at present being completed, consists of the ACFM reported here, which will transmit IOP information to a portable processing unit, which can sample and record pressure once every 2 minutes for a period of several seconds, over 24 hours. The result of each IOP sample will be recorded on the digital memory board.

Information will be read out from the memory board by the computer and recorded on a disc or plotter. Later a microprocessor and simple chart recorder will be substituted for the computer. The size of the portable processing unit will be such that it can be carried on a waist belt, a shoulder strap, in a handbag, or stored on a bedside table at night. There will be no wired connection between the monitor and the portable processor/memory board. The patient will therefore be unencumbered apart from the requirement to carry the processor around with him or have it within 3 to 6 feet (2 to 3 m) from the ACFM, which is placed on the head or can be included on a spectacle frame.

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ADDED IN PROOF. After submission of this paper for publication a reference was found to direct recording of intraocular pressure in man. It reports similar observations to those observed in man by our monitor (Coleman, DJ, Trokel, S. *Arch Ophthalmol* 1969; **82**: 637–40.

British Journal of Ophthalmology, 1979, **63**, 805–807

Retinal vein obstruction and intraocular pressure: abnormal postural response independent of facility of outflow

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SUMMARY Eleven patients with a central retinal vein obstruction and 18 with a tributary vein obstruction were examined. The intraocular pressure of both eyes of each subject was measured while he was in the sitting position and again after he had been lying down for 15 minutes. Tonography was then carried out on both eyes. No correlation was found between the value of the coefficient of outflow and the magnitude of the rise in intraocular pressure occurring in any eye on the adoption of the supine position, and no correlation between the relative values of the coefficients of outflow in any pair of eyes and the occurrence of the obstruction in one eye rather than the other.

In a previous communication (Williams and Peart, 1978) we reported our finding that patients who have suffered a unilateral central or tributary retinal vein obstruction show a bilateral defect in the regulation of their intraocular pressure when they are subjected to a change in posture, namely, when they change from the sitting to the supine position. Thus in the subjects we examined the mean rise of pressure recorded in a group of normal eyes was 0·6±1·2 mmHg, while that recorded in patients with a central vein obstruction was 1·8±2·4 mmHg in the eye with the lesion and 2·6±2·3 mmHg in the contralateral eye and in patients with a tributary vein obstruction 3·1±2·3 mmHg in the eye with the lesion and 2·1±2·2 mmHg in the contralateral eye.

These findings seemed to us to have 2 features of particular significance: (1) the abnormal response was present in both eyes; (2) it was similar to that shown by eyes with chronic simple glaucoma.

In our previous communication we referred to the studies of Inglima (1966), who performed a postural test on both eyes of patients with unilateral simple glaucoma and found an abnormal response in the glaucomatous eye only. His tonographic studies made on a series of normal and glaucomatous eyes showed a significant relationship between the facility of outflow and rise of intraocular pressure in response to change of posture. We also referred to the studies of Vannas and Tarkkanen (1960) and Bertelsen (1961), who performed tonography on both eyes of a number of patients with a unilateral central vein obstruction and found a somewhat superior facility of outflow in the obstructed eyes as compared with the contralateral.

With this work in mind we decided, as an initial investigation of the phenomenon we had found in our patients, to examine a further number of subjects with either a central or tributary vein obstruction in order to find out if they showed a correlation between (1) facility of outflow and magnitude of postural response and/or (2) facility of outflow and site of the obstruction, that is, in one eye as opposed to its fellow.

Patients and methods

We examined 2 groups of patients all of whom had received a preliminary clinical examination. They comprised (1) 11 cases of unilateral central vein obstruction; (2) 18 cases of tributary vein obstruction, 17 of which had a unilateral lesion and 1 a bilateral lesion.

The patients were selected irrespective of age, sex, the supposed aetiology of the obstruction, or the presence of systemic hypertension. The duration of the obstruction varied, and some were receiving coincident systemic therapy with drugs such as hypotensives, diuretics, etc. Two patients with central vein occlusions were receiving local treat-

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ment with pilocarpine drops; in one case to the eye with the obstruction in the other case to the contralateral eye.

The group of patients with central vein obstruction contained 7 males and 4 females. Their ages ranged from 59 to 74 years, mean 67·8 years. The group with tributary vein obstruction contained 14 males, one of whom had bilateral lesions, and 4 females. Their ages ranged from 41 to 79 years, mean 60·4 years.

METHOD

The patient was asked to sit quietly for 15 minutes near one end of an examination couch. Amethocaine 1% drops were then instilled into both conjunctival sacs, and the intraocular pressure was measured with the Alcon Applanation Pneumatonograph, the right eye being examined first. The first 2 tracings were disregarded (Langham, 1974) and a second pair of tracings made 5 minutes later. These were recorded. The patient was then asked to lie down for 10 minutes, when a second pair of tracings from the right and left eyes were recorded. (The value of the intraocular pressure was taken as the mean of the systolic and diastolic values on the tracing of the intraocular pulse.)

Tonography was then performed for 2 minutes on each eye and the coefficient of outflow derived in the usual way.

Results

From Table 1 it will be seen that our patients showed rises of intraocular pressure in response to change of posture, similar to those found in the first series of patients described in our previous paper. Thus in the case of patients with a central vein obstruction the obstructed eyes showed a mean rise of 3·8±2·0 mmHg and the contralateral eye a mean rise of 3·1±2·2 mmHg, while in the case of unilateral tributary vein obstruction the obstructed eyes showed a mean rise of 5·1±3·3 mmHg and the contralateral eyes a mean rise of 3·8±2·6 mmHg. The patient with bilateral lesions showed a rise of 3·5 mmHg in both eyes. As with those found in our first series of patients, these values are patently significant when compared with the mean value of 0·6±1·2 mmHg which we found in normal eyes (Williams and Peart, 1978).

Table 1 *Results of treatment*

	Mean rise of intraocular pressure on lying (mmHg)		*Coefficient of outflow*	
	Obstructed eye	*Fellow eye*	*Obstructed eye*	*Fellow eye*
Unilateral central vein obstruction (11 cases)	3·8±2·0	3·1±2·0	0·3±0·2	0·2±0·1
Unilateral tributary vein obstruction (17 cases)	5·1±3·3	3·8±2·6	0·2±0·1	0·2±0·1

We analysed our results with respect to the following points: (1) the values found for the coefficients of outflow in both eyes of patients with a unilateral obstruction compared with the value 0·15 μl/min/mmHg considered as the lower limit of normal; (2) the relative values for the coefficient of outflow in the obstructed and non-obstructed eye; (3) the relationship of outflow to the magnitude of rise in intraocular pressure associated with change in posture.

In order to find the value of the coefficient of outflow, the pressure of the eye was first recorded. The change in pressure occurring with a 10 g weight in place during the 2-minute tonography was then derived by drawing a straight line through the tonographic tracing and subtracting the pressure shown at the conclusion from the pressure at the beginning of the timed cycle. The simplified tables supplied for use with the Alcon tonometer were then used to find the coefficient of outflow by means of these two values. Our value for the normal is based on the results of studies with the Alcon tonometer (Langham, 1974). A group of normal eyes showed a mean value of 0·28±0·01 μg/min/mmHg, while a group of glaucomatous eyes showed a mean value of 0·16±0·01 μl/min/mmHg.

CENTRAL VEIN OBSTRUCTION

We found that of the 11 cases 6 had coefficients of outflow in both eyes which were within the normal range, that is, greater than 0·15, and in most cases these indicated remarkably free drainage potential. Of the 5 remaining cases 3 showed frankly abnormal values in at least 1 eye. One patient had chronic open-angle glaucoma in his unobstructed eye, the second in her obstructed eye, and the third had no evidence of glaucoma but gave a history of a mother who died blind. A fourth patient, whose values were very near the lower limit of normal, had a pressure of 20 mmHg in the obstructed eye (sitting position), a disc which showed early cupping, and a possible early field defect, but the fifth, whose obstructed eye had a low coefficient, had no evidence of glaucoma and no significant family history.

In 5 cases the facility of outflow was greater in the eye with the venous obstruction than in its colleague and in 5 cases the reverse was true. In one case (the first noted above) the values were equal and abnormal. Hence it appears that the magnitude of the rise of intraocular pressure associated with the change in posture is independent of the facility of outflow.

TRIBUTARY VEIN OCCLUSION

Of the 17 cases of unilateral branch vein obstruction 12 showed facilities of outflow within the normal range in both eyes, and again many of these indicated a remarkably free drainage potential. The remaining 5 all had 1 eye which had an abnormally low value. Of these, 2 had slightly raised pressures (measured in the sitting position), but no other signs of glaucoma—23 mmHg and 20 mmHg. There was no evidence of early glaucoma in any of the remaining 3 patients, but 1 gave a history of a father who had bilateral glaucoma.

In the case of the bilateral lesion both coefficients of outflow were well within the normal limits.

In 8 unilateral cases the facility of outflow was greater in the obstructed eye and in 8 cases the reverse was true. In the patient with bilateral lesions the outflow from one eye was considerably greater than the other (0·48 c/w 0·24), yet the rise of pressure was equal in both eyes (3·5 mmHg).

As in the case of patients with central vein lesions, it appears that the magnitude of the rise of intraocular pressure in response to change of posture is independent of the values of the coefficient of outflow.

Conclusions

Our results show that the abnormal postural pressure results we have found in our patients are independent of the outflow facility. They confirm the results found by Vannas and Tarkkanen (1960) and Bertelsen (1961) for central vein lesions. Patients with retinal vascular obstructive lesions show a postural response similar to that of patients with chronic simple glaucoma but differ from them in that their intraocular pressures are within the normal range when these are measured in the sitting position and may or may not rise into the pathological range when measured with the patient in the supine position. Clearly the stage of a sustained (and rising) intraocular pressure is associated with the presence of an impaired drainage system, but the postural pressure responses in our patients are not.

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British Journal of Ophthalmology, 1979, 63, 808–812

Intraocular pressure reduction in chronic simple glaucoma by continuous infusion of dilute pilocarpine solution

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SUMMARY Ten hospital outpatients with bilateral chronic simple glaucoma received a single drop of 2% pilocarpine to one eye and a continuous infusion of 0·1% pilocarpine at a flow rate of 0·01 ml/min to the other eye (both solutions were at pH 7·2). On another occasion the treatments were reversed. Measurements of intraocular pressure (IOP) and pupil diameter were made at 30 min intervals for 2 hours. The continuous infusion of dilute solution was as effective as the single drop of more concentrated solution in reducing IOP and in constricting the pupil; the drop was somewhat faster in producing its effect.

It has previously been shown in normal persons that the technique of continuous infusion of a dilute solution of pilocarpine at a rate which does not produce overflow from the conjunctival sac can be as effective as a pupilloconstrictor as a single drop of a more concentrated solution (Birmingham *et al.*, 1976a). We now report an investigation of the effectiveness of continuous infusion of dilute pilocarpine in lowering the intraocular pressure in elderly hospital outpatients with chronic simple glaucoma. A preliminary account of this work has been presented elsewhere (Birmingham *et al.*, 1976b).

Patients and methods

The subjects were 10 outpatients of the Glaucoma Clinic at Nottingham Eye Hospital who had a diagnosis of bilateral chronic simple glaucoma which was controlled by pilocarpine eye drops. There were 6 men and 4 women and their ages ranged from 63 to 83 years (mean 71·4 years). They gave their informed consent to participate in a comparison of the effect of a single drop of 2% pilocarpine at pH 7·2 with that of an infusion at 0·01 ml/min of 0·1% pilocarpine at pH 7·2. A cross-over design was used so that each eye received the single drop on one occasion and the infusion on another.

The patients were asked to attend the clinic on 3 separate occasions at weekly intervals. The time of day was the same for each visit to minimise any effect of diurnal variation. At the first visit the patients were on their usual treatment, and 3 measurements of intraocular pressure (IOP) of both eyes were made at 30 min intervals to establish controlled baseline IOP. The patients were asked to stop using their drops for the 3 days preceding each of the next 2 visits. At the second visit, after 1 measurement of IOP and pupil diameter of each eye, an infusion of 0·1% pilocarpine at 0·01 ml/min was begun to the right eye and a single drop of 2% pilocarpine was administered to the left eye. The infusion was continued for 2 hours and readings of IOP and pupil diameter were made for both eyes at 30 min intervals. At the third visit the procedure followed during the second visit was repeated except that the right eye received the single drop administration and the left eye received the continuous infusion. At the end of the third visit the patients were told to return to their usual treatment.

Five healthy volunteers with no history of eye disease except mild refractive errors, who did not wear contact lenses, took part in a separate investigation of the effects on bilateral pupil diameter of an infusion of 0·1% pilocarpine at pH 7·2 for 2 hours into the left eye. Pupil diameter was measured every 5 min.

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MEASUREMENT OF INTRAOCULAR PRESSURE AND PUPIL DIAMETER

For the patients at the Glaucoma Clinic the IOP was measured by applanation tonometry (Goldmann tonometer) under 0·5% proparacaine local anaesthesia. Pupil diameter was measured by direct observation through the calibrated graticule of the telescope of a Goldmann perimeter under controlled white light illumination.

In the normal volunteers the pupil diameter was measured under low intensity red light illumination in a dark room. The pupil was observed through a low-power binocular microscope (×5 eyepieces, ×1·25 objectives) suspended above the eye. One eyepiece was fitted with a graticule to allow direct measurement of the diameter of the pupil in the field of view.

INFUSION TECHNIQUE

This was identical to that described by Birmingham *et al.* (1976a). The solution was contained in a sterile 1 ml syringe compressed by a motor driven syringe ram at a rate to provide a flow of 0·01 ml/min. The fluid was delivered to the conjunctival sac of the eye being infused by means of sterile small-bore silicone elastomer tubing (Silastic No. 602-101, Dow Corning) of about 2 m length. The distal end of the tubing rested in the inner canthus of the eye and was held in place by adhesive tape attached to the nose and forehead.

When a patient needed to move between rooms at ½-hourly intervals for measurements of IOP and pupil diameter, the infusion was briefly interrupted and the syringe was temporarily removed from the syringe ram and clipped to the patient's clothing.

PILOCARPINE SOLUTIONS AND DOSES

The sterile solutions of pilocarpine hydrochloride were specially formulated to a pH of 7·2 by the addition of borate buffer. Owing to the much shorter shelf life of pilocarpine at near neutral pH than at its natural more acid pH (Riegelman and Vaughan, 1958; Cowle and Anderson, 1967) the solution was provided in 2 bottles, the contents of which were mixed immediately before use. One bottle contained the pilocarpine solution at its natural pH at twice the final concentration required, the other bottle contained an equal volume of an appropriate borate buffer and sodium chloride solution. On mixing the 2 solutions, a sterile solution, isotonic with tears, having a pH of 7·2 and pilocarpine concentration of 2% or 0·1% was obtained.

After the recording of baseline measurements the patients received one drop (0·05 ml) of 2% pilocarpine (dose 1 mg) to one eye and the infusion of 0·1% pilocarpine at 0·01 ml/min (dose 1 mg after 100 min) to the other eye. This procedure was reversed for the 2 eyes on the third visit.

The normal subjects received only the 0·1% pilocarpine infusion to the left eye on 1 occasion.

Results

COMPARISON OF THE OCULAR HYPOTENSIVE EFFECTS OF PILOCARPINE AT PH 7·2 GIVEN AS A SINGLE DROP OR AS AN INFUSION

The means of the 3 measurements of IOP made on both eyes when the 10 patients were on their usual treatment for their glaucoma were 18·8 mmHg for right eyes and 19·1 mmHg for left eyes (Table 1). After stopping the treatment for 3 days, on 2 occasions at weekly intervals, the IOP rose in both eyes. The rise in pressure in the right eyes was statistically significant; the rise in pressure in the left eyes was smaller and did not achieve statistical significance (Table 1).

The single drop of 2% pilocarpine and the continuous infusion of 0·1% pilocarpine reduced the IOP of both eyes and the effect increased with time over the period of observation (Fig. 1). At each 30 min point of measurement after the start of treatment the means of the differences between pretreatment measurements and post-treatment measurements for either the single drop or the continuous infusion were statistically significant (Table 2). When the effects of the 2 treatments were compared, the degree of fall in pressure at each time of measurement was the same in the left eyes whether they had received the drop or the infusion. For the right eyes the fall in pressure was greater at 30 and at 60 mm for the drop compared with the infusion (this difference was statistically significant

Table 1 *Means (with one standard deviation) for right and left eyes (n=10) of intraocular pressure measurements made while taking standard treatment and after interrupting treatment for 3 days*

	1st Visit, While receiving usual drops	*2nd Visit, 3 days after stopping drops*	*3rd Visit, 3 days after stopping drops*
Right eyes (n=10)	18·8 (4·5)	24·7 (5·8)	25·3 (5·1)
Left eyes (n=10)	19·1 (3·9)	21·3 (3·3)	22·4 (3·0)

	Differences (paired t tests) between:	
	1st and 2nd Visits	*1st and 3rd Visits*
Right eyes	0·02>P>0·01	0·02>P>0·01
Left eyes	0·2>P>0·1	0·1>P>0·05

only at 60 min) but was not greater at 90 and 120 min. Thus it appears that the rate of effect and the degree of effect of the 2 treatments were the same in left eyes, whereas in right eyes the rate of onset of effect was greater for the single drop but the eventual degree of effect was no different from that achieved by the infusion.

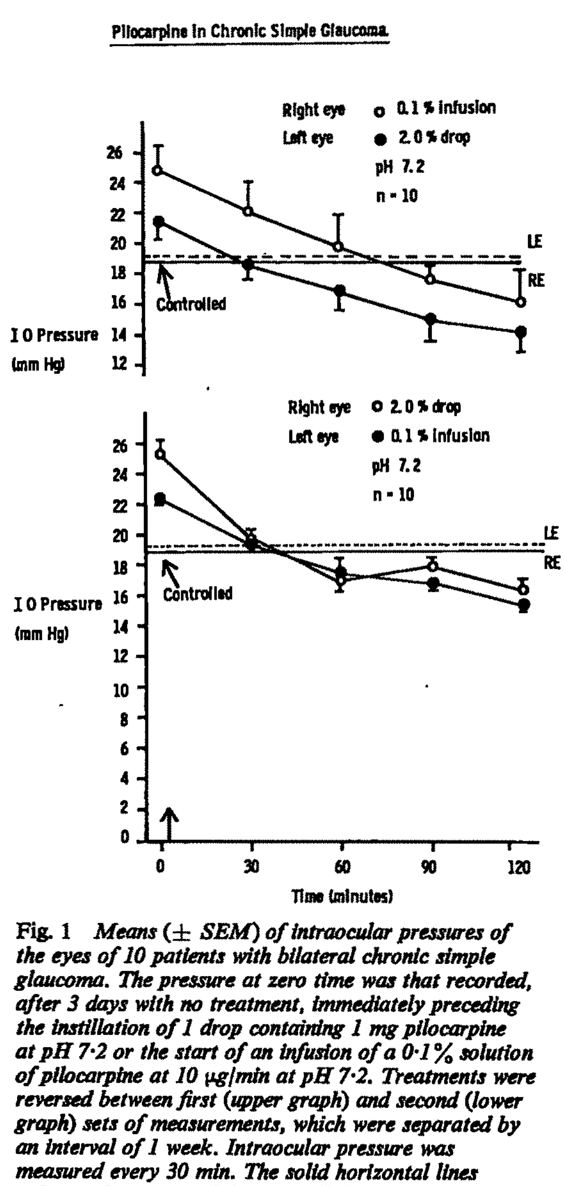

Fig. 1 *Means (± SEM) of intraocular pressures of the eyes of 10 patients with bilateral chronic simple glaucoma. The pressure at zero time was that recorded, after 3 days with no treatment, immediately preceding the instillation of 1 drop containing 1 mg pilocarpine at pH 7·2 or the start of an infusion of a 0·1% solution of pilocarpine at 10 µg/min at pH 7·2. Treatments were reversed between first (upper graph) and second (lower graph) sets of measurements, which were separated by an interval of 1 week. Intraocular pressure was measured every 30 min. The solid horizontal lines indicate the means of the controlled intraocular pressures of right eyes (RE) on regular treatment with pilocarpine drops and the broken horizontal lines those for left eyes (LE)*

EFFECT ON PUPIL DIAMETER

For the patients the effect of either treatment was to reduce pupil diameter. This reduction was statistically significant at the first post-drug measurement at 30 min for all eyes and remained so for the next 3 measurements (Table 3). When the treatments were compared, there was a significantly greater pupilloconstrictor effect from the drop than from the infusion in left eyes at 60 min only and in right eyes at 60 and at 90 min (notes a, b, and c, Table 3).

For the 5 normal subjects an infusion of 0·1% pilocarpine to the left eye rapidly reduced pupil diameter to a mean of some 30% of control diameter by 50 min after the start of the infusion. This reduction persisted until the cessation of the infusion. Throughout the 120 min of infusion to the left eyes there was no change in diameter of the pupils of the untreated right eyes.

Discussion

From this comparison of 2 methods of administering pilocarpine the general conclusion seems to be that a continuous infusion of a dilute solution is as effective as a single drop of a more concentrated solution. For a fair comparison of the 2 methods it was necessary to administer the same dose to each eye. When the interruptions of the infusion which were necessary for IOP and pupil diameter measurements are taken into account, the dose delivered by the 2% drop or the 0·1% infusion was the same at 1·0 mg. Because of the pronounced influence of pH on pilocarpine absorption (Anderson and Cowle, 1968; Birmingham *et al.*, 1976a) it was necessary to make the pH of both the concentrated drop and the dilute infusion the same (pH 7·2) at a value close to that of tears.

It is unlikely that the patients' usual treatment was still exerting an effect 3 days after stopping the drops. Drance *et al.* (1974) showed that 15 h after the high dose of a drop of 8% pilocarpine the IOP had returned to within 90% of the pre-drug value. After stopping the usual treatment for 3 days the expected difference in pressure between the 2 eyes was found. Davanger (1965) in an extensive study reported a mean difference in pressure between the 2 eyes of patients with glaucoma of 2·8 mmHg. In the present small series the mean differences were 3·4 mmHg at the second visit and 2·9 mmHg at the third visit.

The appropriateness of a 2 h period for the measurement of the effects of the treatments is supported by the finding of Drance and Nash (1971), who measured the effect of 2% pilocarpine for 8 hours but found the effect to be maximal at 2 hours. Fenton and Schwartz (1963) found the

Table 2 *Means (with standard deviation) for the right and left eyes of differences between IOP (mmHg) after interrupting treatment for 3 days and IOPs at 30, 60, 90, and 120 min after beginning of infusion or application of drop. The same 10 patients attended for the 2nd and 3rd visits*

		2nd Visit		
	30 min	*60 min*	*90 min*	*120 min*
Right eyes (n=10) (0·1% infusion)	2·6 (3·0)	4·9 (2·8)	7·3 (3·4)	8·7 (2·6)
Paired t-test	0·025>P>0·02	P<0·001	P<0·001	P<0·001
Left eyes (n=10) (2·0% drop)	2·5 (3·1)	4·3 (2·3)	6·3 (3·8)	7·0 (4·0)
Paired t-test	0·05>P>0·025	P<0·001	P<0·001	P<0·001
		3rd Visit		
	30 min	*60 min*	*90 min*	*120 min*
Right eyes (n=10) (2·0% drop)	5·8 (6·6)	8·3 (4·5)	7·5 (4·8)	9·0 (4·7)
Paired t-test	0·025>P>0·02	P<0·001	P<0·001	P<0·001
Left eyes (n=10) (0·1% infusion)	2·7 (3·4)	5·0 (3·9)	5·8 (3·2)	7·1 (3·5)
Paired t-test	0·05>P>0·025	0·005>P>0·001	P<0·001	P<0·001

Table 3 *Means (with one standard deviation) for right and left eyes of pupil diameters (mm) after interrupting treatment for 3 days and at 30, 60, 90, and 120 min after beginning of infusion or application of drop. The same 10 patients attended for the 2nd and 3rd visits*

			2nd Visit		
		Time after exposure to drug			
	Pre-drug	*30 min*	*60 min*	*90 min*	*120 min*
Right eyes (n=10) (0·1% infusion)	3·3 (0·6)	2·2 (0·6)	2·1 (0·5)	2·0 (0·5)	1·9 (0·5)
Paired t-test		P<0·001	P<0·001	P<0·001	P<0·001
Left eyes (n=10) (2·0% drop)	3·2 (0·7)	2·3 (0·8)	1·9 (0·7)^a	1·9 (0·7)	1·9 (0·7)
Paired t-test		0·02>P>0·01	0·005>P>0·001	0·005>P>0·001	0·005>P>0·001
			3rd Visit		
Right eyes (n=10) (2·0% drop)	3·3 (0·7)	1·9 (0·6)	1·7 (0·5)^b	1·7 (0·5)^c	1·7 (0·5)
Paired t-test		P<0·001	P<0·001	P<0·001	P<0·001
Left eyes (n=10) (0·1% infusion)	3·2 (0·5)	2·6 (0·6)	2·3 (0·6)	2·2 (0·6)	2·1 (0·7)
Paired t-test		0·005>P>0·001	P<0·001	0·005>P>0·001	0·005>P>0·001

Within eyes there was a significantly greater pupilloconstrictor effect of the 2% drop compared with the 0·1% infusion at 60 min (a, 0·05>P>0·025; b, P<0·001) for both eyes and at 90 min (c, 0·025>P>0·02) for right eyes.

effect of 2% pilocarpine to reach 'a steady state' at 75 min in 10 patients with glaucoma. Thus in the present investigation the effect of the infusion was compared at 2 hours with the likely maximal effect of the single drop. At the end of this 2 hour period the hypotensive effect of the 2 treatments was similar: in right eyes the mean falls in IOP were 8·7 mmHg for the infusion and 9·0 mmHg for the drop, in left eyes the corresponding values were 7·1 and 7·0 mmHg. The rate of achievement of this fall was greater for the drop than for the infusion in right eyes but the same in left eyes.

Change in pupil diameter was measured as another index of entry of drug into the eye. Again the effect of the 2 treatments was similar at the end of 2 hours: in right eyes the mean pupilloconstrictor effects were 1·4 mm for the infusion and 1·6 mm for the drop, while the corresponding figures for left eyes were 1·1 and 1·3 mm. During the 2 hour period the greater effect of the drop at 60 min (both eyes) and at 90 min (right eyes only) suggests a faster rate of effect for the drop.

It is not surprising that there were some differences in the rate of onset of effect. Although the final dose at the end of 2 hours was the same, the initial concentration produced by the 2% drop would be higher than that produced by the 0·1% infusion. Schumacher (1966) found that pilocarpine (pH 4·2) could be detected in the aqueous of rabbits within 3–5 min of instillation of a single drop into the conjunctival sac. Van Hoose and Leaders (1974) suggested that the release of drug from the endothelial surface of the cornea depended on the concentration of the drug to which the cornea was exposed. The cornea was seen to act as a reservoir for the drug. The effectiveness of a 2% drop will decline after 2 hours (Drance and Nash, 1971), whereas that of an infusion will continue for as long as the infusion is continued.

The observations on the time course of the effects of a single drop or an infusion on IOP and pupil diameter in patients with glaucoma are consistent with those for pupil diameter in normal subjects. Birmingham *et al.* (1976a) found the maximum effect of a single drop of 0·5% pilocarpine to be the same as that of an infusion of 0·01% pilocarpine but to occur 30 min earlier.

The study of the effects of administering pilocarpine to 1 eye showed that there was no detectable effect of that administration on the contralateral untreated eye. It seemed justifiable therefore to investigate different treatments to each of the 2 eyes on 1 occasion in the knowledge that there would be little or no interference between eyes.

We conclude from our results that a continuous infusion of a dilute solution of pilocarpine into the conjunctival sac is as effective in lowering the IOP in glaucoma as a more concentrated solution administered as a drop. The use of dilute solutions of pilocarpine would seem to be likely to reduce the possibility of systemic toxicity. To the advantage of the continuous maintenance by the infusion of an effective concentration in the eye for as long as the infusion is continued may be added the reduction in disturbance of the patient and the reduced nursing time compared with the frequent administration of drops. The principle of continuous infusion is obviously applicable to drugs other than pilocarpine. The use of a small body-borne infusion device allows the patient some degree of mobility during treatment (Bedford *et al.*, 1976).

We thank the patients who co-operated in this investigation and the nursing staff of Nottingham Eye Hospital for their help and forbearance.

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Control of glaucoma by reduced dosage guanethidine-adrenaline formulation

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SUMMARY The effect of formulations of guanethidine and adrenaline of different composition has been tested in rabbits and in patients with glaucoma. The concentrations of guanethidine and adrenaline used for the rabbits were 5·0% and 1·0%; 2·5% and 0·5%; 1·0% and 0·2%; 0·5% and 0·1%. All except the lowest combination were equally effective in the magnitude of the decrease in intraocular pressure brought about and in their duration of activity. Two formulations containing guanethidine and adrenaline at concentrations of 3·0% and 0·5% and 1·0% and 0·2% respectively (formulated as Ganda drops by Smith and Nephew Pharmaceuticals Ltd) were tested in a blind, cross-over, short-term clinical trial on 20 patients. The drops containing the lower concentration of drugs were as effective as those of higher concentration. These results lead us to believe that most patients who respond to this treatment could be put on a reduced dosage regimen, which should result in a decreased incidence and severity of side effects.

Guanethidine and adrenaline are now well established in the treatment of glaucoma, and we have previously shown (Jones *et al.*, 1977) that it was possible to manage glaucoma in some patients with this combination of drugs over a 5-year period. The drugs were instilled separately, guanethidine 5% first followed by adrenaline 1% 30 minutes afterwards. Although it was possible to avoid the routine use of miotics by this method, the treatment led to the development of a number of side effects, in particular conjunctival hyperaemia, pupillary dilatation, catarrh, and sinusitis. Moreover a number of patients developed resistance to these drugs over a 3-year period and had to have their therapy changed.

We showed in an acute clinical trial (Jones *et al.*, 1977) that guanethidine 3% and adrenaline 0·5% was as effective clinically as guanethidine 5% and adrenaline 1%. This trial also showed that the drops were equally effective when given as a single formulation as when instilled separately, which confirmed an earlier study with rabbits (Jones *et al.*, 1975). Several clinical studies have indicated that they may be more effective in combination than alone (Patterson and Patterson, 1972; Roth, 1973; Gloster, 1974). A formulation of guanethidine 3% and adrenaline 0·5% is now available as Ganda 305 and there have been favourable reports on its use in glaucoma (Mills and Ridgway, 1978; Hoyng and Dake, 1979; Romano and Patterson, 1979). The latter workers did not encounter any instances of tachyphylaxis or resistance in their trials over 6 months. Side effects are reduced but are still present, and our clinical experience shows that conjunctival hyperaemia and pupillary dilatation in particular cause inconvenience to a significant proportion of patients.

We have therefore investigated the possibility of reducing the concentration of the drugs further to see whether the incidence of side effects might be reduced while leaving the therapeutic efficiency unchanged. This paper reports the results of experiments performed with rabbits on guanethidine/adrenaline drops of different concentrations and also on a short-term clinical trial on 20 glaucoma patients comparing the efficacy of guanethidine/adrenaline in concentrations of 1·0 and 0·2% w/v respectively with 3·0 and 0·5% w/v.

Rabbit experiments

The experimental animals were 12 male New Zea-

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land white rabbits aged between 5 and 8 months. They were conditioned to having eye drops instilled into their eyes and having their intraocular pressure (IOP) measured at intervals throughout each working day for 1 month before the experiment began.

IOP measurements were taken with the rabbits in a holding box, a Perkins hand-held applanation tonometer being used. Benoxinate 0·4% w/v was instilled into each eye as a local anaesthetic before the measurements were taken.

For the assessment of activity of the different dosage forms the rabbits were divided into 4 groups of 3. Each member of each group was given 1 drop of the test formulation in one eye and 1 drop of sterile saline in the other. IOP measurements were then performed on both eyes at regular intervals over 48 hours. The rabbits were allowed 5 clear days between treatments, and then the groups were rotated. In this way over 4 weeks each group of 3 rabbits received each of the 4 experimental formulations. The results were calculated as a reduction in IOP using the untreated eye as a control and then expressed as an average response for the 12 rabbits. The experimental justification for this protocol and treatment of results has been given previously (Jones *et al.*, 1975).

Four different formulations were used, differing only in the amounts of guanethidine sulphate and adrenaline hydrogen tartrate. The drops were prepared in Kolthoff's borate-phosphate buffer at pH 7·4 and contained 0·01% w/v benzalkonium chloride and 0·1% w/v sodium metabisulphite. The drops were sterilised by filtration through a 0·22 μm membrane filter and packed aseptically into sterile 10 ml glass bottles. The different formulations contained the amounts of guanethidine and adrenaline shown in Table 1.

The results obtained for the 4 treatments are given in Fig. 1 as a mean reduction in IOP for the 12 rabbits with readings taken at 0, 2, 5, 10, 25, 30, and 35 hours. The IOP of all rabbits had returned to normal after 48 hours.

Although the period of activity in rabbits is much longer than that reported for man, we nevertheless believe that the rabbit is a reasonable model for comparing the efficiency of different formulations. It is clear that there is little difference in therapeutic efficiency between any of these formulations, the weaker solutions having an entirely satisfactory onset, intensity, and duration of activity in comparison with the stronger solutions. There is, however, some indication that the intensity of effect elicited by the weakest formulation containing 0·5% guanethidine and 0·1% adrenaline is less than the others. It was decided therefore to test the efficiency of guanethidine 1·0% and adrenaline 0·2% in patients and compare it to that of one of the commonly used combination strengths.

Table 1 *Drug composition in the experimental formulation*

Formulation	*A*	*B*	*C*	*D*
% w/v Guanethidine sulphate	5·0	2·5	1·0	0·5
% w/v Adrenaline hydrogen tartrate	1·0	0·5	0·2	0·1

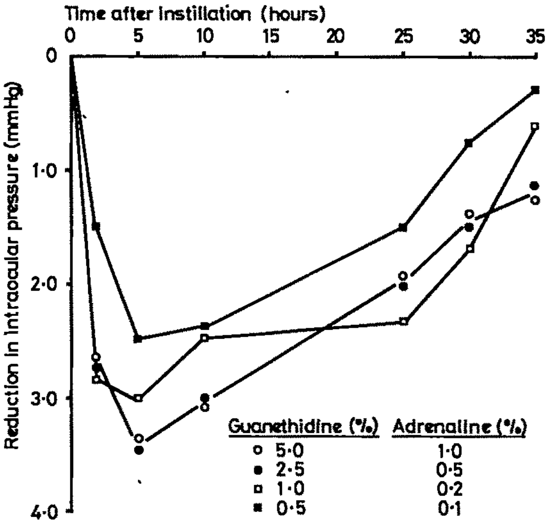

Fig. 1 *Effect of formulations containing different concentrations of guanethidine and adrenaline on the intraocular pressure of rabbits*

Clinical trials

Two different formulations were used, differing in their concentrations of active drugs. One contained 1·0% guanethidine and 0·2% adrenaline, the other 3·0% and 0·5%. Both formulations were prepared at our request by Smith and Nephew Pharmaceuticals Ltd as experimental solutions packed in plain 10 ml plastic bottles with an integral dropper. In each case the vehicle was the ordinary vehicle used for their marketed drops under the trade name Ganda.

The trial was carried out on 2 successive Saturdays on a group of 20 patients who had been under treatment for simple open-angle glaucoma for at least 2 years. Ten of the patients were male, 10 female, and their ages ranged from 55 to 81. Their normal treatment varied but all were placed on pilocarpine alone for 1 week before the trial and for the week between the 2 experimental Saturdays. They continued to use the appropriate strength of

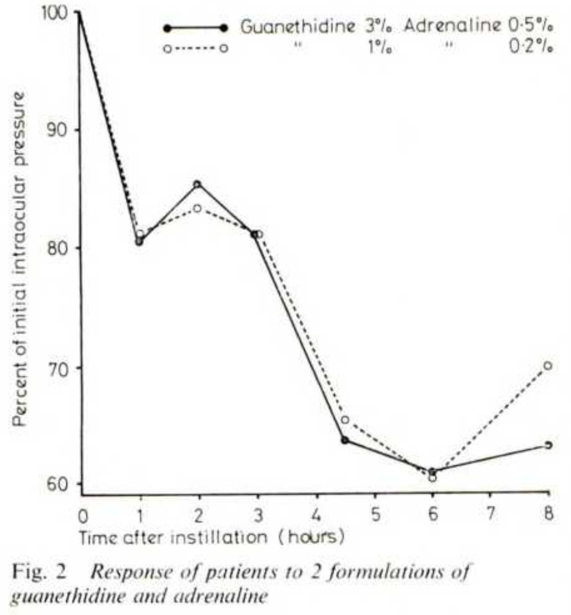

Fig. 2 *Response of patients to 2 formulations of guanethidine and adrenaline*

pilocarpine eye drops until 6 pm on the Friday evenings before the 2 days of the trial, when all therapy was suspended. Their uncontrolled IOP, as measured on the days of the trial with a Goldmann applanation tonometer, ranged from 16 to 48 mmHg, with the majority being in the upper 20s. They were divided randomly into 2 groups of 10.

On the days of the trial the IOP of each patient was taken by one of us (DEPJ), and each patient then received in both eyes drops of one or other of the experimental formulations. Neither the patients nor DEPJ knew which patients received which drops, and the order in which the patients were treated was randomised. Their IOPs were measured after 1, 2, 3, 4½, 6, and 8 hours and the results recorded. At the time of each reading the state of the patient's eyes was noted and his subjective opinion on any effect was also recorded. The formulations received by the patients were different on each of the 2 days of the trial so that a normal, blind, cross-over trial was performed.

The results were expressed for each eye as a percentage reduction of the initial reading; each eye therefore acted as its own control. A full description of the rationale behind this treatment has been given previously (Jones *et al.*, 1977). Inspection of the data for each week indicated no difference in the response of the 2 groups, so that the results from both days were pooled. Each experimental period therefore is the mean of 40 readings. These results are shown in Fig. 2.

The data show clearly that with these patients the low-concentration drops are as effective in terms of onset of activity and intensity of action as the high-concentration drops. It may be that the duration of activity is slightly less, though this is not yet clear, and the clinical significance of any small difference in duration is likely to be negligible. The side effects noted were hyperaemia and pupil dilatation. In the first week 1 patient on the low-dosage drops had pupil dilatation while 5 on the high-dosage drops experienced these effects. Of these 5, 4 also had pupil dilatation during the second week, and these were joined by 4 others now receiving the high dosage, including the patient who responded to the low dosage in week 1. The incidence of hyperaemia was low in week 1, only 5 patients having a noticeable response. However, in week 2, 10 patients had a significant hyperaemia, the response being apparently unconnected with the dosage received.

It should be remembered that all these patients were being subjected to the trauma of IOP readings on seven occasions during the day, which might also have played a part in this observed response. No significant subjective changes were volunteered by the patients except that, in week 1, two patients on the low dosage complained of a transient headache. As they did not complain in week 2 when receiving the high dose these side effects can probably be ignored.

As we have found in all our trials using adrenaline the response is in two stages, there being an initial fail followed by a rise and then a second fall in IOP. These 2 effects are probably due to the 2 reported actions of adrenaline, namely, in reducing production of aqueous humour and in stimulating outflow, having different time responses. The transient increase in pressure after 2 hours may be the consequence of pupillary dilatation in some persons. A similar effect has been reported by Hoyng and Dake (1979).

The significant findings from these experiments is that, as measured by the response of this group of patients, the drops containing the low concentration of both guanethidine and adrenaline are as effective in reducing IOP as the high-concentration drops. It should be possible, therefore, to put patients who respond to this treatment on to a reduced dosage regimen, which should be beneficial to them in terms of their ability over a long period to tolerate the treatment.

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Acute closed-angle glaucoma: an investigation into the effect of delay in treatment

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SUMMARY A retrospective study of 212 eyes with acute closed-angle glaucoma is reported. A peak incidence in the sixth decade was noted and an increased incidence in females confirmed statistically. A surprising and often marked delay occurred in the presentation of many patients for treatment, but visual outcome was not influenced by such delay. Despite good control of intraocular pressure, many of the eyes suffered visual loss from optic nerve damage, and the visual outcome was not related to the height of intraocular pressure at presentation. Damage to the visual system occurred very early in the disease, probably with the initial acute rise of intraocular pressure, and eyes appear to vary in their susceptibility to such an insult. It does not appear that earlier presentation of the patient with acute glaucoma would significantly improve the visual outcome in terms of visual acuity. The short critical time before damage occurs to the eye suggests a role for preventive ophthalmology in the detection and surgery of eyes at risk with shallow anterior chambers and narrow angles before they develop acute closed-angle glaucoma.

Acute glaucoma has long been known as a potentially blinding disease which was at first incurable, but treatment became possible just over a century ago with the introduction of iridectomy and miotics. The disease is regarded as an ophthalmological emergency, and the lowering of the intraocular pressure to physiological levels is considered a matter of urgency to minimise visual loss. Modern management involves initial medical control of the intraocular pressure with pilocarpine, acetazolamide, and osmotic diuretics followed by iridectomy or fistulising surgery when the pressure has been controlled. Several studies have confirmed a significant risk of acute glaucoma following in the fellow eye when treated conservatively (Bain, 1957; Lowe, 1962; Ghoshal and Blaxter, 1969), and so consideration is given to the need for prophylactic peripheral iridectomy in that eye also. In view of the severe pain and marked fall in vision which occurs in acute closed-angle glaucoma it is surprising for how long many patients tolerate the disease before presenting for treatment.

This study was undertaken to assess the effect of delay in patient presentation, to seek a critical time within which the disease should be controlled for best visual result, and to assess the results of the modern management of acute closed-angle glaucoma.

Material and methods

This study was made retrospectively by review of the case notes of 191 patients who presented with acute closed-angle glaucoma in the years 1971–74 and who have been the subject of a previous study of aetiological factors (Hillman and Turner, 1977).

Results

Of the 191 patients included in the study 21 (11·0%) presented with bilateral acute glaucoma, giving a total of 212 eyes studied; 60 (31·4%) of the patients were male and 131 (68·6%) female, and their ages ranged from the fourth to the ninth decade (Fig. 1). In comparison with population statistics for 1971 a chi-squared analysis shows a statistically significant increased proportion of females ($P<0.001$). The number of days the patients tolerated the disease before presentation appears in Fig. 2, which shows that 30·9% presented on the first day and progressively smaller numbers on the succeeding days, with a second peak of presentation after a week.

The visual acuities of the eyes on presentation are compared with their final visual acuities in Fig. 3,

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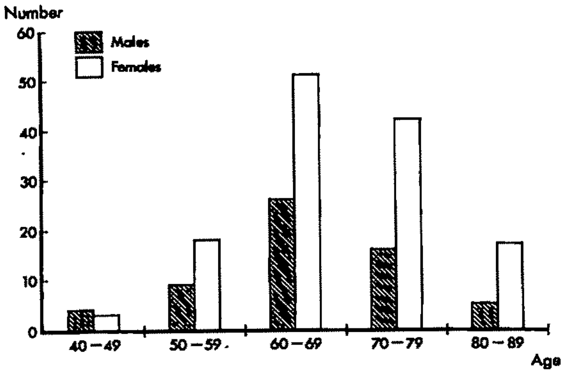

Fig. 1 *Sex and age distribution of 191 patients with acute closed-angle glaucoma*

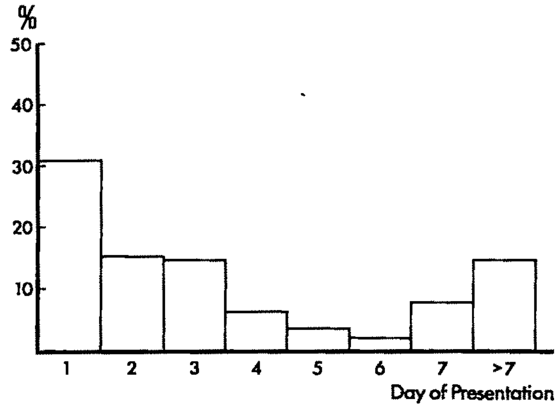

Fig. 2 *Delay in presentation by patients with acute closed-angle glaucoma*

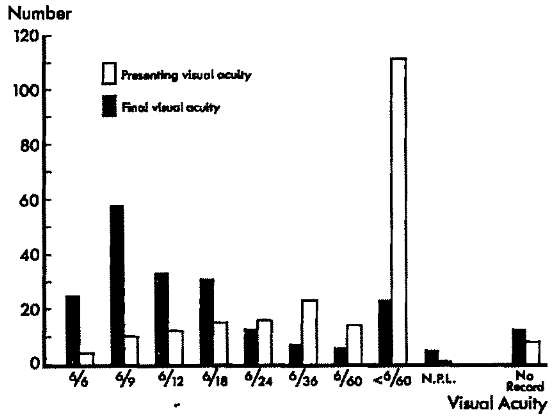

Fig. 3 *Presenting visual acuity compared with final visual acuity in eyes treated for acute closed-angle glaucoma*

which shows that 158 (74·5%) of these eyes regained '6/18 or better' vision, 127 (59·9%) regained '6/12 or better', and only 23 eyes (10·8%) achieved 6/6 vision. The response of these eyes to the initial medical treatment is shown in Table 1. In 156 (73·6%) eyes control of intraocular pressure was achieved by acetazolamide together with pilocarpine delivered as drops or by a saturated hydrophilic contact lens (Hillman *et al.*, 1975). In a further 53 (25·0%) eyes control was achieved by the added use of oral glycerol and in only 3 (1·4%) eyes medical control failed. Table 2 shows that the response to medical control was not directly related to the level of intraocular pressure on presentation.

Surgery was performed as shown in Table 3 on all eyes except 10, when the patients refused surgery

Table 1 *Response of 212 eyes with acute closed-angle glaucoma to initial medical treatment*

Medical treatment	*1971*	*1972*	*1973*	*1974*	*1971–74*
Control by pilocarpine and acetazolamide	30	30	51	45	156 (73·6%)
Control by pilocarpine, acetazolamide, and glycerol	18	4	15	16	53 (25·0%)
Failed medical control	0	3	0	0	3 (1·4%)

Table 2 *Response of eyes with acute closed-angle glaucoma to initial medical therapy considered with regard to the height of intraocular pressure on presentation*

Presenting IOP	*Pilocarpine and acetazolamide* (%)	*Pilocarpine, acetazolamide, and glycerol* (%)	*Failed control* (%)
20 to 40 mmHg	81·3	18·7	—
41 to 60 mmHg	71·9	26·5	1·6
61 to 70+ mmHg	73·9	23·9	2·2

Table 3 *Surgical procedures performed after medical control of 212 eyes with acute closed-angle glaucoma*

Surgical treatment	*1971*	*1972*	*1973*	*1974*	*1971–74*
Peripheral iridectomy	23	17	35	33	108 (50·9%)
Trabeculectomy	12	14	25	18	69 (32·6%)
Broad iridectomy	11	0	1	2	14 (6·6%)
Lens extraction	0	3	2	4	9 (4·2%)
Scheie's procedure	0	1	1	0	2 (0·9%)
No surgery	2	2	2	4	10 (4·7%)

Table 4 *Final visual acuities achieved for each day of presentation of 212 eyes with acute closed-angle glaucoma*

Day	*6/6*	*6/9*	*6/12*	*6/18*	*6/24*	*6/36*	*6/60*	*<6/60*	*Blind*	*No record*
1	7	23	7	6	6	3	2	6	0	3
2	2	9	5	6	0	2	1	4	0	3
3	3	8	11	5	2	1	1	2	0	0
4	2	1	5	2	1	0	1	0	1	0
5	0	3	0	3	1	0	0	1	0	0
6	0	2	1	1	1	0	0	0	0	0
7	2	3	0	2	1	0	0	2	3	2
>7	6	9	2	2	1	0	1	7	1	4
No record	1	0	2	4	0	1	0	1	0	1

or were considered too ill. As the patients were under the care of a number of different surgeons varying criteria were applied to select the type of surgery, and approximately one-half of the eyes had peripheral iridectomy and approximately one-third had trabeculectomy.

Consideration was next given to the spectrum of visual outcome for each day of presentation (Table 4) and also to the proportion of eyes achieving '6/12 or better' vision for each day of presentation (Fig. 4). There is a significant regularity of results which appears independent of the day of presentation for treatment. In view of this, consideration was given to the presenting visual acuities of those eyes which presented promptly on day 1 compared with those which presented late on day 7 or later and which finished with visual acuity '6/12 or better' (Fig. 5). It is interesting that there is no significant difference in the presenting visual acuities associated with this delay in presentation for treatment. The same applies to the comparison of presenting visual acuities for eyes which presented early or late and finished with visual acuity 'worse than 6/12' (Fig. 6).

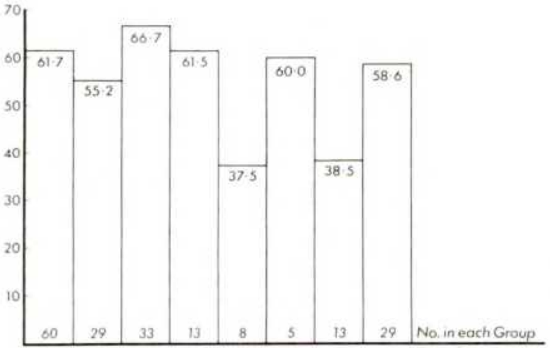

Fig. 4 *Proportion of eyes with acute closed-angle glaucoma which achieved final visual acuity '6/12 or better' for each day of presentation*

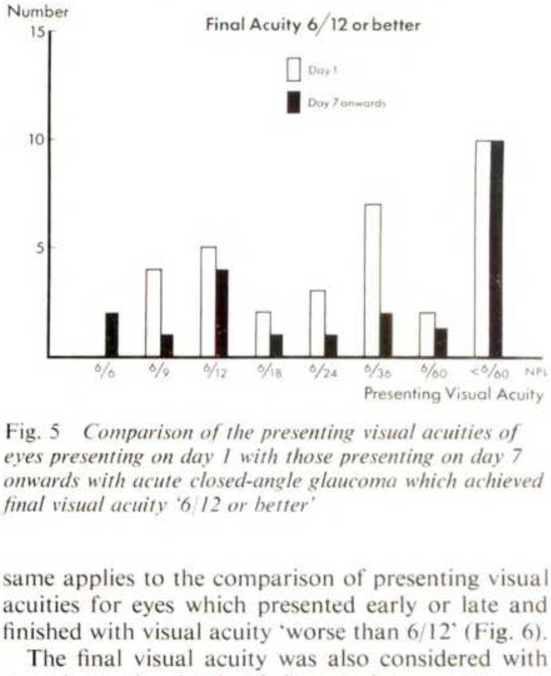

Fig. 5 *Comparison of the presenting visual acuities of eyes presenting on day 1 with those presenting on day 7 onwards with acute closed-angle glaucoma which achieved final visual acuity '6/12 or better'*

The final visual acuity was also considered with regard to the level of intraocular pressure on presentation, and Fig. 7 shows that there appears to be no strong relationship.

In this series 34 eyes (16·0%) had a poor outcome with final visual acuity '6/60 or worse' despite apparently good medical and surgical control of the intraocular pressure in most cases. Table 5 presents the apparent reasons for poor vision in these eyes. The major cause of glaucomatous visual loss appeared to be atrophic change in the optic nerve, and this was not associated with very high intraocular pressure on presentation. Of these 19 eyes 10·5% presented with pressures between 20 and 40 mmHg, 63·2% presented with pressures between

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41 and 60 mmHg, and 21·0% presented with pressures between 61 and 70+ mmHg. As expected in an elderly population of patients a number of eyes had coexisting disease—macular degeneration, cataract, arterial occlusion, and in 1 case amblyopia. Three eyes in this series failed to recover from hyphaema associated with trabeculectomy surgery.

Discussion

The statistically significant predominance of females over males and the peak incidence in the sixth decade is as expected from clinical experience with acute glaucoma. The sexual difference is attributable to the shallower anterior chamber in the female as shown in optical and ultrasound studies (Törnquist, 1953; Jansson, 1963). The 11·0% of bilateral cases in this series is similar to the 8·5% reported by Bain (1957) and the 11·5% reported by Lowe (1962) in series of similar size.

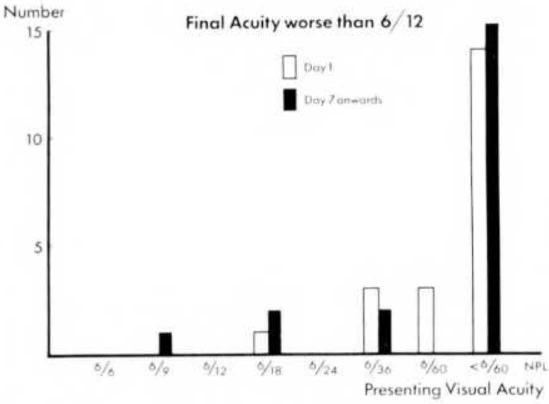

Fig. 6 *Comparison of the presenting visual acuities of eyes presenting on day 1 with those presenting on day 7 onwards with acute closed-angle glaucoma which achieved final visual acuity 'worse than 6/12'*

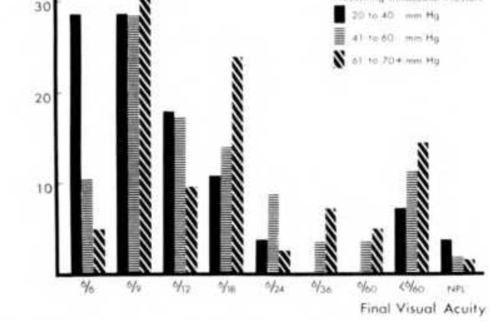

Fig. 7 *Final visual acuity for eyes with acute closed-angle glaucoma considered with regard to the height of intraocular pressure on presentation*

Table 5 *Reasons for poor visual outcome in 34 eyes which achieved final visual acuity '6/60 or worse' after acute closed-angle glaucoma*

Blind (5 eyes)	Optic atrophy		2
	Trabeculectomy haemorrhage		2
	Other pathology		1
	retinal detachment	1	
6/60 or less (29 eyes)	Optic atrophy		17
	Trabeculectomy haemorrhage		1
	Other pathology		11
	macular degeneration	4	
	cataract	3	
	arterial occlusion	1	
	amblyopia	1	
	mental confusion	2	

At the time of presentation most of the patients had severe reduction in visual acuity to about 6/60 or less and only 12·3% with 6/12 or better. Most of the patients responded well in terms of control of intraocular pressure to both the initial medical and later surgical treatment, the response to initial treatment being independent of the height of intraocular pressure on presentation. After this apparently successful treatment, however, only 74·5% eyes achieved 6/18 or better vision, only 59·9% eyes achieved 6/12 or better, and only 10·8% achieved 6/6 vision. These figures may be compared with the 76·7% which achieved 6/18 or better in the series of Mackie and Rubinstein (1954) and the 84% which achieved 6/12 or better in the small series reported by McNaught *et al.* (1974).

Table 4 shows that there is a group of eyes which presented late after 1 week but did particularly well, achieving visual acuities of 6/6 or 6/9. These have behaved differently from the main population and are possibly cases of subacute closed-angle glaucoma rather than true acute closed-angle glaucoma. The overall unsatisfactory visual results despite apparently good response of intraocular pressure to treatment demonstrate the permanent damage which occurs to the visual system in most cases and which is marked in some.

The patients show a surprising and often considerable delay in presentation, with less than one-third presenting on the first day of the attack. The average delay of 3·5 days is less than the delay of 10·9 days reported by Lloyd (1948) and may reflect an improvement in patient education. It is interesting to consider the eyes which achieved a good visual outcome with regard to this delay in presentation. Fig. 4 shows that approximately 60% of eyes achieved 6/12 or better irrespective of the day of presentation. The eyes which did well presented with a similar spectrum of visual acuities whether they presented on the first day or the seventh day of the attack. There was no association between the height of the intraocular pressure on presentation and visual outcome. Consideration of the 16% of eyes which had a bad visual outcome suggested that the main cause of visual loss in acute glaucoma is neuronal damage.

The independence of visual outcome from the speed of presentation of the patient suggests that neuronal damage occurs very early in the disease, possibly within hours of the initial high rise in intraocular pressure. The independence from the height of intraocular pressure at the time of presentation suggests that there is individual variation in the ability of different eyes to withstand the insult of sudden pressure rise just as eyes differ in their ability to withstand the sustained pressure rise of chronic glaucoma.

The risk to the 'fellow' eye in acute glaucoma is well appreciated, and the place for prophylactic peripheral iridectomy is firmly established. The results of this study show that earlier presentation of the patient would not significantly improve the visual outcome in the eye with acute glaucoma. The short critical time before damage occurs to the eye suggests a role for preventive ophthalmology in the detection and surgery of 'first' eyes which have shallow anterior chambers and narrow angles placing them at risk before they develop acute closed-angle glaucoma.

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Management of acute closed-angle glaucoma with miotics and timolol

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SUMMARY The hypotensive effect of intramuscular or intravenous acetazolamide with frequent instillation of 2% or 4% pilocarpine in polyvinyl alcohol, or with single drops of pilocarpine in polyvinyl alcohol or oily vehicles, and the hypotensive effect of topical timolol alone and together with pilocarpine was investigated in the treatment of acute closed-angle glaucoma in 75 patients (81 eyes). The results showed that there was no marked difference in the hypotensive effect whether pilocarpine was used frequently or in a single dose, in different concentrations, or in different vehicles after acetazolamide. Topical timolol alone was not effective enough to control the intraocular pressure in acute closed-angle glaucoma, but a good hypotensive effect was seen when topical timolol was followed by pilocarpine. It is concluded that 1 drop of pilocarpine 3 hours after intravenous or intramuscular acetazolamide or after topical timolol may be sufficient to terminate an acute attack. Topical timolol may serve as a valuable alternative when systemic medication is contraindicated.

The initial treatment of acute closed-angle glaucoma (CAG) is directed towards lowering intraocular pressure (IOP) by medical means to avoid operating upon a congested eye. This is usually achieved with carbonic anhydrase inhibitors, osmotic agents, and pilocarpine. Miotics may be used with frequent instillation, or once 3 or 4 hours after intravenous acetazolamide (Ganias and Mapstone, 1975). Pilocarpine is usually administered in polyvinyl alcohol (PVA) or methyl cellulose vehicles. Application of pilocarpine in oil produces an increased hypotensive effect in open-angle glaucoma (Saari *et al.*, 1978b). The effect of pilocarpine in oily drops has not been studied in CAG. A beneficial effect from a pilocarpine-soaked hydrophilic lens in the management of CAG has been reported (Hillman, 1974; Hillman *et al.*, 1975).

A new beta-adrenergic blocking agent, timolol maleate, lowers the IOP effectively in primary open-angle glaucoma (Zimmerman and Kaufman, 1977; Boger *et al.*, 1978; Airaksinen, 1979) and in secondary glaucoma (Saari *et al.*, 1978a) but not in capsular glaucoma (Kerty and Hørven, 1978; Airaksinen, 1979). It reduces IOP by suppressing the formation of the aqueous humour (Zimmerman *et al.*, 1977). Goethals and Missotten (1977) reported 2 patients with CAG who were treated with topical timolol after maximal acetazolamide and pilocarpine therapy. There are no other reports on the hypotensive effect of timolol in CAG.

In this study we examined the hypotensive effect of acetazolamide with pilocarpine, which was used in different concentrations and vehicles and with different instillation frequencies, and of topical timolol alone and together with pilocarpine.

Material and methods

Seventy-five patients (81 eyes) with CAG, 13 males and 62 females, age range 33 to 85 (mean 62) years, were included in the study. The patients were treated in one of the following 7 ways: (1) Intramuscular acetazolamide 500 mg, and 2% pilocarpine hydrochloride solution in 1·4% PVA instilled every 15 min for 2 hours and then every hour (Table 1, cases 1–26, 28 eyes with CAG). Together with systemic acetazolamide, glycerol was given perorally to 14 patients (Table 1, cases 13–26). (2) Intramuscular acetazolamide 500 mg, and 4% pilocarpine hydrochloride in 1·4% PVA instilled every 15 min for 2 hours and then every hour (Table 2, cases 27–50, 25 eyes). (3) Intramuscular acetazolamide 500 mg,

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Table 1 *Hypotensive effect of acetazolamide and 2% pilocarpine (group 1) in CAG*

Case	*Age*	*Sex*	*Duration (days)*	*Initial IOP(mmHg)*	*Final IOP(mmHg)*	*Time (h)*
1	77	F	1	84	21	5
2	61	F	1	84	16	8
3	70	F	1	70	15	5
4	58	M	5	56	16	5
5	85	F	7	70	21	6
6	73	F	1	44	16	6
7	41	F	2	52	18	1
8	76	F	1	70	10	5
9	55	F	1	50	17	2
10	64	F	1	62	16	3
11	49	F	1	50	19	2
12	55	M	7	70	18	4
13	63	F	1	80	12	5
14	74	M	7	70	20	6
15	68	F	1	80	*64*	8
16	61	F	4	54	18	3
17	69	F	3	76	13	3
18	46	F	1	70	29	3*
19	40	M	1	58	10	8
20R	53	M	1	65	11	2
L	53	M	1	65	11	2
21	45	F	1	54	*54*	9
22	60	F	1	64	12	6
23R	47	F	1	50	11	2
L	47	F	1	69	11	2
24	62	F	1	70	16	2
25	46	F	1	70	21	7
26	62	F	1	62	*55*	10

* Operated at 3 hours.

and 2% pilocarpine in a castor oil vehicle repeated once after 2 hours (Table 3, cases 51–61, 12 eyes). Four patients (Table 3, cases 56–59) received together with acetazolamide intravenous mannitol infusion and 2 patients (Table 3, cases 60–61) glycerol perorally. (4) Two drops of 0·5% timolol within 1 hour (Table 4, cases 62–68 ,7 eyes). (5) Two drops of 0·5% timolol within 1 hour and 3 hours later 1 drop of 2% pilocarpine (Table 5, cases 69–73, 6 eyes with CAG). (6) A 59-year-old woman (case 74) with a duration of symptoms for 2 weeks and with initial IOP of 80 mmHg in the right eye and 76 mmHg in the left was treated with intravenous acetazolamide 250 mg followed by 4% pilocarpine in PVA every 15 min for 2 hours into the right eye; a hydrophilic contact lens presoaked in 1% pilocarpine was applied onto the left eye. (7) A 78-year-old woman (case 75) with duration of symptoms for one day had initial of IOP 76 mmHg in the right eye. She was treated with intravenous acetazolamide 500 mg followed by 1 drop of 4% pilocarpine in PVA 3 hours later.

The treatment was considered a failure if after 8 hours IOP was greater than 21 mmHg.

Results

The results for the treatment groups are given in Tables 1–5. The duration indicates the time between onset of acute symptoms and start of therapy. Initial IOP was measured before the treatment began. Final IOP was the lowest recording at the time stated after starting treatment.

Group 1 had 3 obvious failures (cases 15, 21, and 26) and 1 patient (case 18) was operated on at 3 hours when the IOP was 29 mmHg; all these patients had received glycerol perorally together with intramuscular acetazolamide. Group 2 had 3 failures (cases 41, 43, and 49); in case 43 the IOP was 26 mmHg at 8 hours and 9 hours later 16 mmHg. Group 3 had 3 failures; 1 of these (case 56) had received mannitol together with acetazolamide.

Group 4 had 4 failures (cases 64 and 66–68). In case 66 the IOP was 28 mmHg at 8 hours and

Table 2 *Hypotensive effect of acetazolamide and 4% pilocarpine (group 2) in CAG*

Case	*Age*	*Sex*	*Duration (days)*	*Initial IOP(mmHg)*	*Final IOP(mmHg)*	*Time (h)*
27	52	F	1	80	11	5
28	69	F	1	84	14	3
29	69	F	1	67	11	7
30	58	F	3	80	10	8
31	61	M	1	59	14	4
32	60	M	1	82	13	3
33	61	F	2	59	21	8
34	63	F	2	70	18	5
35	55	F	1	60	21	8
36	61	F	1	80	12	8
37	61	F	1	80	7	4
38	61	F	2	54	9	4
39	63	F	1	82	8	3
40R	50	F	6	80	12	2
L	50	F	6	80	12	2
41	66	F	3	80	*68*	8
42	33	M	7	64	14	2
43	65	F	4	51	*26*	8
44	66	F	1	55	16	3
45	56	F	1	70	19	6
46	76	F	1	60	15	8
47	58	F	2	80	17	3
48	58	F	7	63	15	4
49	46	F	1	80	*80*	5
50	72	F	1	54	7	5

Table 3 *Hypotensive effect of acetazolamide and oily drops of 2% pilocarpine (group 3) in CAG*

Case	*Age*	*Sex*	*Duration (days)*	*Initial IOP(mmHg)*	*Final IOP(mmHg)*	*Time (h)*
51	61	F	3	56	20	2
52	80	F	1	80	*69*	4
53R	57	F	1	80	14	2
L	57	F	1	54	14	2
54	64	F	1	59	20	8
55	76	F	1	82	*40*	8
56	76	F	1	80	*40*	8
57	69	F	7	75	11	6
58	49	F	1	70	13	2
59	55	M	2	56	16	2
60	72	F	2	52	10	3
61	49	M	2	72	21	8

Table 4 *Hypotensive effect of timolol (group 4) in CAG*

Case	*Age*	*Sex*	*Duration (days)*	*Initial IOP(mmHg)*	*Final IOP(mmHg)*	*Time (h)*
62	54	M	1	50	18	4
63	58	M	2	59	18	1
64	79	F	1	60	*36*	8
65	66	F	1	56	21	8
66	53	M	3	65	*28*	8
67	63	F	5	60	*38*	4
68	58	F	1	68	*80*	3

Table 5 *Hypotensive effect of timolol and 2% pilocarpine (group 5) in CAG*

Case	*Age*	*Sex*	*Duration (days)*	*Initial IOP (mmHg)*	*IOP at 3 h (mmHg)*	*Final IOP (mmHg)*	*Time (h)*
69R	81	F	7	69	43	*26*	8
L	81	F	7	69	37	21	8
70	77	F	1	59	55	*26*	8
71	63	F	1	70	55	17	4
72	78	F	2	62	46	*42*	8
73	60	F	20	54	42	21	8

6 hours later 20 mmHg. In case 67 the IOP was 38 mmHg at 4 hours and the patient was given 500 mg acetazolamide perorally; 8 hours later the IOP was 18 mmHg. A good hypotensive effect of timolol was seen in cases 62, 63 and 65; in case 65 gonioscopic examination showed that the chamber angle was still occluded.

In group 5 all cases showed decrease of IOP 3 hours after timolol (Table 5) and subsequent pilocarpine caused reduction to normal of IOP in 3 eyes (cases 69 left eye, 71, and 73). Gonioscopic examination was performed for case 73, which revealed an open chamber angle. In case 69 the reduction of IOP was considered sufficient also in the right eye, and both eyes were successfully operated on. In case 70 the IOP was 26 mmHg and in case 72 it was 42 mmHg at 8 hours; in both cases the IOP was 15 mmHg 12 hours later.

The 59-year-old woman (case 74) with bilateral CAG had a final IOP of 12 mmHg at 2 hours in both the right eye treated with intensive instillation of 4% pilocarpine and the left eye treated with a pilocarpine presoaked hydrophilic contact lens. In the right eye of the 78-year-old woman (case 75) treated with 1 drop of 4% pilocarpine 3 hours after acetazolamide the final IOP was 16 mmHg at 8 hours after starting the treatment.

Discussion

The results indicate that frequent instillation of 4% pilocarpine (Table 2) does not have a greater hypotensive effect in CAG than 2% pilocarpine (Table 1). Therefore 4% pilocarpine should not be used, because excessive use of pilocarpine may produce toxic side effects (Epstein and Kaufman, 1965). To diminish the frequency of instillations and the total dose of pilocarpine in the treatment of CAG the use of a pilocarpine-soaked hydrophilic contact lens has been suggested. This method is as effective as intensive medication with 4% pilocarpine (Hillman, 1974); we could observe this in 1 patient.

The instillation frequency may also be reduced by oily drops of pilocarpine, which have a strong and long-lasting miotic effect (Borgmann and Wurster, 1973; Saari *et al.*, 1978c; Smith *et al.*, 1978) and may provide a more conventional and less expensive alternative than a pilocarpine-soaked hydrophilic contact lens in the treatment of CAG. In this study 1 or 2 oily drops of pilocarpine administered after intramuscular acetazolamide had a good hypotensive effect in 9 of 12 eyes. Ganias and Mapstone (1975) observed that 1 drop of pilocarpine 3 hours after intravenous acetazolamide suffices to stop the attack. A similar observation was made in this study when pilocarpine-PVA drops were used.

In CAG miotics will not cause the ischaemic sphincter to react until the IOP is lowered by other means (Rutkowski and Thompson, 1972). In this study intramuscular or intravenous acetazolamide followed by pilocarpine had a good hypotensive effect in CAG, but additionally given peroral glycerol did not improve the results (Table 1, cases 13–26).

Topical timolol maleate reduces IOP by suppressing aqueous humour production nearly as effectively as systemic carbonic anhydrase inhibitors (Coakes and Brubaker, 1978), but in contrast to these and osmotic agents topical timolol has no appreciable side effects. In this study 2 drops of timolol had a good hypotensive effect in 3 cases with CAG, and topical timolol followed 3 hours later by pilocarpine reduced the IOP to normal levels in all cases during an extended observation period.

On the basis of the results of this study and of an earlier report (Ganias and Mapstone, 1975) it is sufficient to treat patients with CAG with intramuscular or intravenous acetazolamide 500 mg and 3 hours later by a single drop of pilocarpine. When the patient cannot be treated with systemic medication, it seems appropriate to substitute topical timolol for acetazolamide to reduce the IOP to a level where the sphincter starts to react and then give pilocarpine to open the occluded chamber angle.

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Stickler's syndrome and neovascular glaucoma

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SUMMARY A case of Stickler's syndrome with neovascular glaucoma is described.

Wagner (1938) described a Swiss family with dominantly inherited vitreoretinal degeneration, and von Böhringer *et al.* (1960) re-examined the family, adding further members. The characteristic findings which Wagner described were an optically empty vitreous with peripheral avascular membranes, peripheral visual field constriction, narrowing and sheathing of the peripheral retinal arteries with pigment clumping adjacent to the abnormal vessels and elsewhere in the periphery, choroidal vascular sclerosis and atrophy, myopia, and disc pallor in advanced cases. Presenile posterior subcapsular cataracts were present in some patients while in others these had become mature. None of the patients described by Wagner (1938) and subsequently by von Böhringer and others (1960) were reported to have retinal detachment, and yet further families have been described in whom the risk of retinal detachment was high and the results of treatment poor. Many authors (Delaney *et al.*, 1963; Alexander and Shea, 1965; van Balen and Falger, 1970; Hirose *et al.*, 1973; Tolentino *et al.*, 1976) have advocated early prophylactic surgery prior to the onset of cataracts, which occur consistently by the fifth decade of life (Hirose *et al.*, 1973). The concept has now evolved that there are separate conditions in which the fundus changes are similar. In Wagner's syndrome myopia is of a low degree, cataracts occur in middle life, and the risk of retinal detachment is small. By contrast, families in which retinal detachments are common have high myopia and associated skeletal abnormalities. In some families the skeletal abnormalities are characterised by changes similar to Marfan's syndrome with arachnodactyly, lax joints, and micrognathia; severe arthropathy, cleft palate, and neurosensory deafness have also been described. This condition has been termed Stickler's syndrome (Stickler *et al.*, 1965; Stickler and Pugh, 1967; Opitz *et al.*, 1972; Popkin and Polomeno, 1974).

Open-angle glaucoma has been described (Jansen, 1962; Delaney *et al.*, 1963; Hirose *et al.*, 1973) in some cases, and Frandsen (1966) reported congenital angle anomalies in others.

It is the purpose of this paper to describe a patient with a family history of retinal detachment who presented with neovascular glaucoma in addition to other changes identical to those described by Wagner, and to discuss the aetiology of the glaucoma and the management of the disease in this case.

Case history

A 32-year-old woman of German descent was first seen in the casualty department on 4 May 1978. For the previous 2 months she had experienced transient obscurations of vision in the right eye, which became constantly blurred 10 days before presentation. A diagnosis of neovascular glaucoma had been made at another hospital and treatment started with acetazolamide. Despite this she had developed severe pain in the eye 5 days later, and 2 days before presentation a haemorrhage had been noted in the anterior chamber. Her general health was good, and her only recent medications had been the oral contraceptive pill, which was stopped in January 1978.

Vision with the right eye was 1/60, with a relative afferent pupil defect, and with the left 6/9 corrected by a –6·50 D sphere. The conjunctiva on the right was intensely injected with corneal epithelial oedema. There was a 2 mm hyphaema with rubeosis iridis and ectropion of the iris pigment epithelium; the intraocular pressure was 45 mmHg. No view of the fundus was possible, but ultrasonography showed that the retina was flat. The left anterior segment was normal, as was the drainage angle, the intraocular pressure being 10 mmHg. The left lens had scattered cortical and posterior subcapsular opacities, the latter associated with anterior vitreous attachments. The mid vitreous was optically empty, and there were peripheral vitreous veils. The optic disc and macula were normal, but the peripheral retinal vessels were narrowed and sheathed with

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perivascular pigment clumping. Elsewhere in the peripheral retina there was extensive lattice degeneration and pigmentary change, but no holes were found (Fig. 1). Iris fluorescein angiography showed no abnormality in the left eye (Fig. 2), but fundus angiography showed widespread vascular changes in the periphery, consisting of delayed perfusion of the retina, areas of non-perfusion, and telangiectasis, with considerable dye leakage (Fig. 3). The capillary pattern in the posterior pole was normal. General examination showed no abnormality except arachnodactyly; there was no carotid bruit.

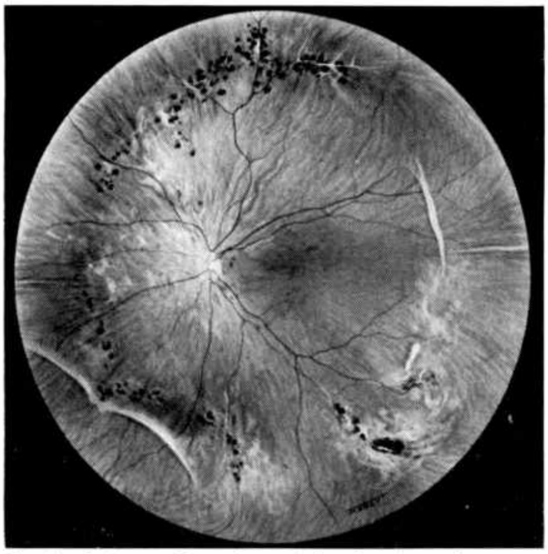

Fig. 1 *Left eye. Extensive peripheral perivascular pigment clumping and vitreous veils*

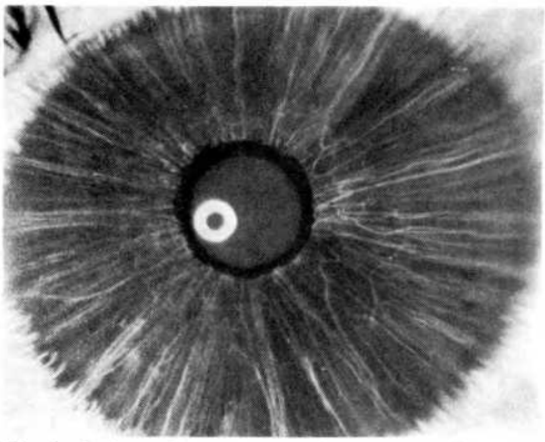

Fig. 2 *Left eye. Iris angiogram showing normal vascular pattern with no leakage of dye*

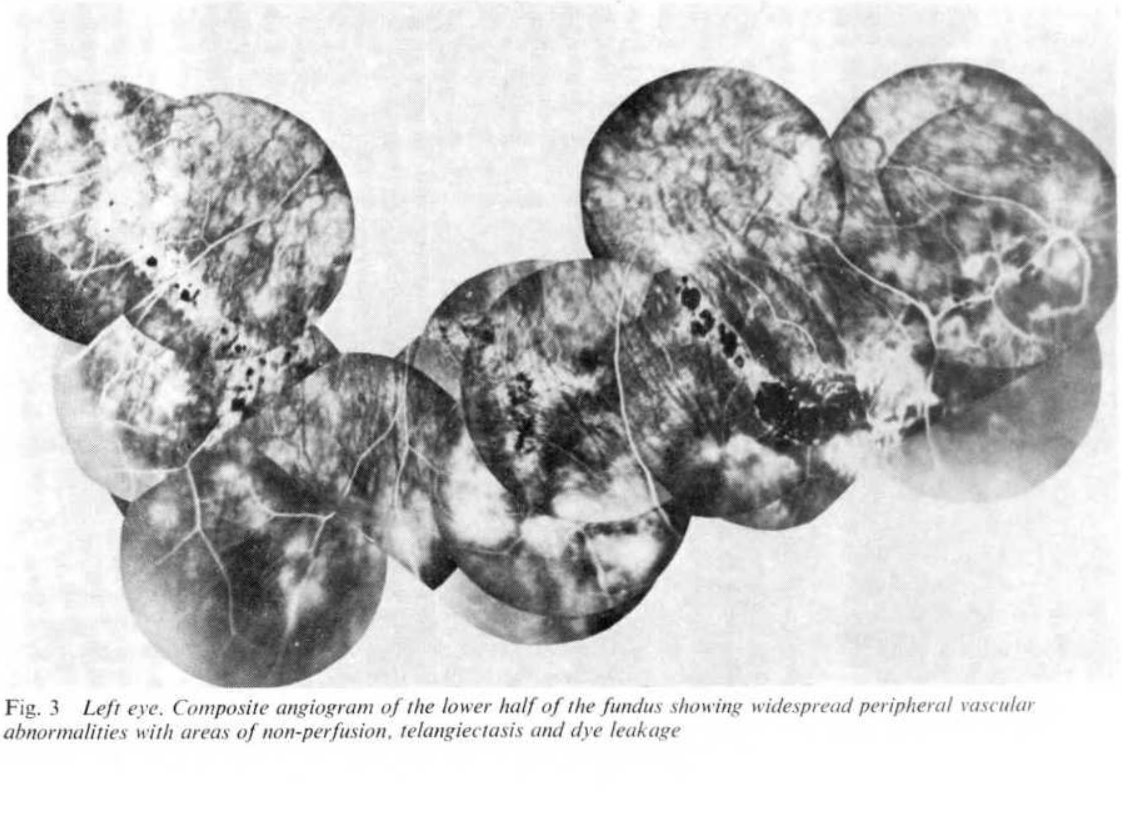

Fig. 3 *Left eye. Composite angiogram of the lower half of the fundus showing widespread peripheral vascular abnormalities with areas of non-perfusion, telangiectasis and dye leakage*

FAMILY HISTORY (Fig. 4)

The patient's mother (III/6) was blind after failed operations for retinal detachment when aged 38 and 45 years, and her sister (IV/6) had one phthisical eye after a similar failure, the other showing vitreous and retinal changes identical to those in our patient's left eye. The affected uncle (III/1) is blind in both eyes, but further details are not available as he lives abroad. The maternal grandfather (II/1) and 2 of his brothers (II/3 and II/6) were blind by middle life.

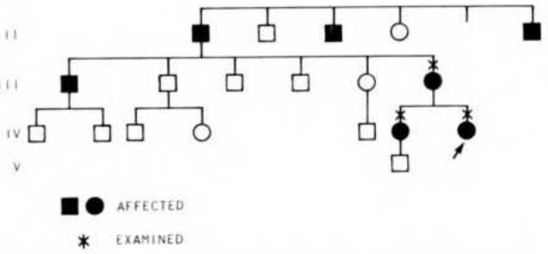

Fig. 4 *Pedigree demonstrating the autosomal dominant inheritance*

INVESTIGATIONS

Urea and electrolytes, glucose tolerance test, plasma proteins, and immunological screen were normal. Serological tests for syphilis were negative. A full blood count showed no abnormality, with a normal film and haemoglobin electrophoresis. Chest and skull *x*-rays were normal, as was an electrocardiogram. Ophthalmodynamometry gave similar readings in each eye.

PROGRESS

She was symptomatically improved on atropine and dexamethasone drops and acetazolamide. On 9 May 1978 the hyphaema had settled, and gonioscopy showed that the angle in the right eye was closed throughout 360°. The fundus was not clearly visible at this time, but an area of yellow exudate was seen in the periphery below. The intraocular pressure remained at 40 mmHg, and on 17 May 1978 a silicone tube was inserted into the anterior chamber under a scleral flap, draining into the upper fornix (Blach *et al.*, 1977). Postoperatively the tube retracted beneath the conjunctiva, and the intraocular end became impacted in the angle below (Fig. 5), but the pressure remained within normal limits for the next month. Thereafter it rose to 30 mmHg, requiring the addition of guanethidine and adrenaline drops to control it. After the introduction of the tube the iris new vessels regressed, and after an initial hyphaema there has been no further bleeding,

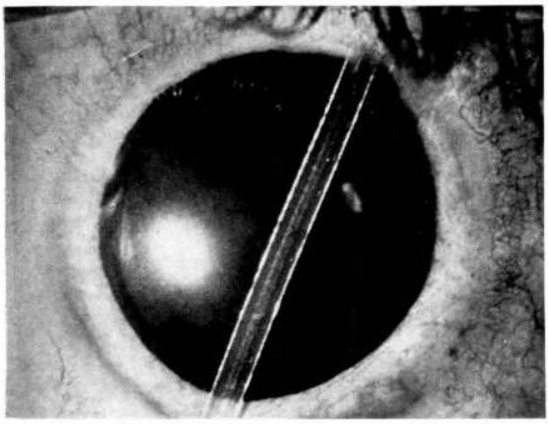

Fig. 5 *Right eye. Tube traversing the anterior chamber becoming impacted in the angle below*

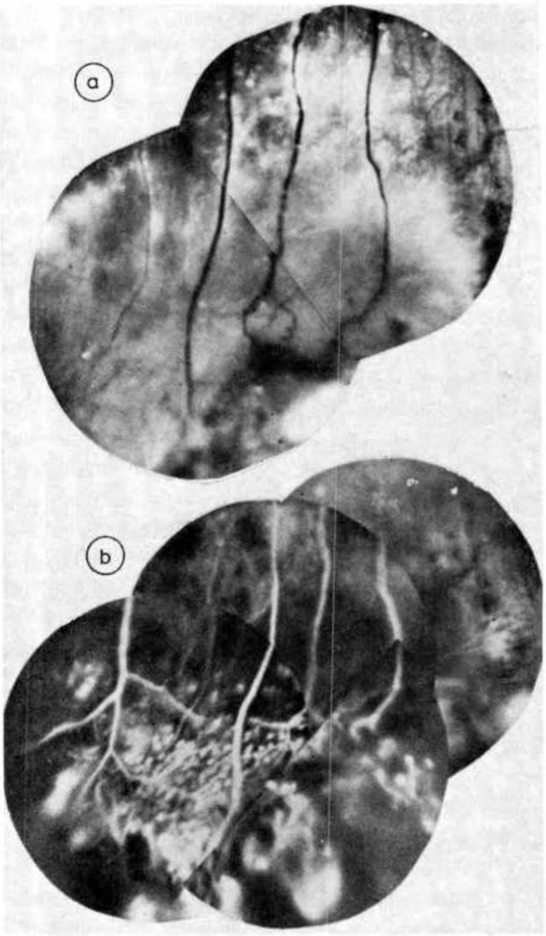

Fig. 6 *Right eye. Colour photograph showing peripheral vascular abnormalities and exudation* (6a) *with telangiectasis confirmed on angiography* (6b)

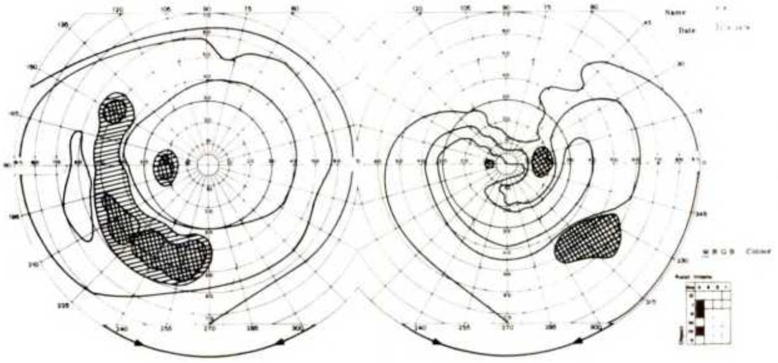

Fig. 7 *Visual fields showing mid-peripheral scotomata in the temporal field of each and constriction of the upper half of the right*

the eye remaining free of pain and without signs of inflammation. The right vision improved to 6/9 despite the development of posterior subcapsular lens opacities. The vitreous and peripheral retina showed changes similar to the left, but the area of telangiectasis was more extensive and associated with considerable exudate below (Fig. 6a). Fluorescein angiography confirmed the abnormal vasculature below, with much dye leakage in the late stages (Fig. 6b).

Visual fields on 21 September 1978 showed scotomata in the mid-temporal periphery of each eye with constriction of the upper field in the right eye (Fig. 7).

On 8 November 1978 an encircling procedure was performed on the left eye which resulted in considerable relaxation of the vitreous traction. The vision in this eye was 6/9 and the intraocular pressure 12 mmHg when last seen. A postoperative iris angiogram showed no change in the vascular pattern.

Discussion

Iris neovascularisation has not previously been reported in Stickler's syndrome. In general it is assumed to be a response to ischaemia (Knox, 1965; Hart and Haworth, 1971) and occurs in patients with widespread capillary non-perfusion in diabetes mellitus (Kohner *et al.*, 1976) and central retinal vein occlusion (Laatikainen and Kohner, 1976), where there is peripheral vessel closure as in Eales's disease (Smith, 1955) and retrolental fibroplasia (Reese and Blodi, 1951), and in cases of reduced perfusion of the eye due to carotid insufficiency (Smith, 1962; Hart and Haworth, 1971), pulseless disease (Knox, 1965), and giant cell arteritis (Wolter and Phillips, 1965). It is also seen in long-standing retinal detachment (Zollinger, 1952). In retinal telangiectasis iris new vessels are rarely seen, and in the original series reported by Coats (1908) 3 of the 6 eyes had secondary glaucoma due to neovascularisation of the angle, but these were the eyes with the most severe retinal disease causing retinal detachment.

In our case the relevance of these factors is uncertain. Peripheral retinal non-perfusion, though present, was confined to the pre-equatorial fundus; the telangiectasis was limited in extent and not associated with retinal detachment. The only other possible contributing factor was myopia, in which the peripheral vessels appear attenuated, but how this affects retinal perfusion is at present poorly documented (Deutman, 1977), and it is not known if this attenuation results in ischaemia. No case has yet been reported of iris new vessels developing in the presence of uncomplicated myopia.

It is possible that the combination of peripheral vessel closure, retinal telangiectasis, and myopia had an additive effect. However, an additional factor in this patient which at present remains undetected may have precipitated neovascularisation in the anterior segment; alternatively there may be an inherent tendency for this complication in Stickler's syndrome. The lack of previous reports on this subject suggests that it is not a common complication, but 2 cases are described (Alexander and Shea, 1965) in which blind eyes were enucleated after raised intraocular pressure and which showed signs suggestive of iris neovascularisation on histological examination.

This case presented 2 management problems, the first being the control of her glaucoma and the second prophylaxis for retinal detachment.

Treatment of secondary glaucoma due to a neovascular process involving the drainage angle depends on the degree of angle closure. Laatikainen (1977) has shown in central retinal vein occlusion that, in the early stages with an open or partially open angle, panretinal photocoagulation is effective in reducing the pressure and the extent of the rubeosis. When the angle is closed, as in this case, surgical procedures must be adopted to reduce the pressure and maintain vision. Of the noninvasive techniques available cyclocryotherapy is considered to be the most effective by some authors (Feibel and Bigger, 1972; Krupin *et al.*, 1978), but visual deterioration is an almost constant feature, hypotony occurs in one-third of cases, and there is a risk of anterior segment ischaemia (Krupin *et al.*, 1977) and phthisis bulbi (Feibel and Bigger, 1972). Furthermore the pressure control may be only temporary owing to regrowth of the ciliary epithelium (Smith *et al.*, 1977). In this patient the apparently normal posterior pole suggested a good visual prognosis, and because of the complications of cyclocryotherapy we were reluctant to undertake this procedure. Standard filtering procedures are seldom effective as fibrovascular tissue blocks the sclerostomy, but, if used, Scheie's operation may be successful (Watson, 1972), and good results have been reported with sclerotomy combined with β-irradiation (Cameron, 1973). Molteno *et al.* (1977) have reported good results using a seton to drain aqueous into the subconjuctival space. This concept was modified by Blach *et al.* (1977), and their technique was successfully performed in our case, achieving adequate pressure control and maintenance of central vision for 9 months. The lens in this eye is now showing early posterior subcapsular opacities which are distant from any possible site of impaction by the tube. There are certainly adequate causes for lens opacities in this patient apart from the tube. Cataracts are known to develop as part of the disease (Wagner, 1938), and in addition there has been a period of raised intraocular pressure and evidence of anterior segment ischaemia, both of which may have contributed to their development.

Prophylactic measures to reduce the risk of retinal detachment are universally advocated in the literature, and, as detachment operations had failed in all the eyes in members of the family examined by us, they were clearly desirable in our patient. Because of the extensive circumferential vitreous traction, encirclement was considered the ideal procedure. However, the presence of peripheral vascular abnormalities and indirect evidence of anterior segment ischaemia in the right eye indicated that such a procedure might carry a very high risk, since it is known that encirclement itself can cause ischaemia (Boniuk and Zimmerman, 1961; Hudson *et al.*, 1973). With these considerations in mind, and having ensured that there was no evidence of anterior segment ischaemia in the left eye, we undertook a gentle encirclement.

It appears that iris neovascularisation can occur in Stickler's vitreoretinopathy, although the causal relationship between the 2 is unclear. Our findings suggest that before prophylactic measures are undertaken it may be important to investigate the vascular status of the anterior segment, though Hirose *et al.* (1973) reported no ischaemic complications following surgery. We are still considering the more complex problem of prophylaxis for the right eye.

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Transient open-angle glaucoma associated with sickle cell trait: report of 4 cases

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SUMMARY Four black patients, all with sickle trait (SA), developed transient open-angle glaucoma with blood in Schlemm's canal. In 3 patients the condition followed blunt trauma, while in the fourth no antecedent trauma was described. The intraocular pressure became normal in all 4 cases with the resolution of the haemorrhage from the trabecular meshwork and Schlemm's canal.

Sickle cell trait, the commonest of the sickle haemoglobinopathies, affects approximately 9% of the black population of North America.[1] A variety of ocular abnormalities[2–18] have been reported to occur in patients with sickle cell trait. These have included proliferative retinopathy, chorioretinal scarring, spontaneous vitreous haemorrhages, central retinal artery occlusion, angioid streaks, conjunctival vascular abnormalities, and transient open-angle glaucoma. We herewith report 4 additional cases of transient open-angle glaucoma which occurred in patients with sickle trait. In 3 patients the glaucoma followed blunt trauma with microscopic hyphaema, while in the fourth patient a microscopic haemorrhage appeared in Schlemm's canal spontaneously. All patients had blood in the trabecular meshwork or the canal of Schlemm on gonioscopy, and the glaucoma resolved concomitantly with clearing of blood from these areas.

Case reports

CASE 1

A 53-year-old black woman had a history of 3 episodes of blurred vision in the right eye associated with halos around lights for a 4-week period. These episodes lasted several hours each and were not accompanied by pain, injection, or other ocular symptoms. The patient had hypertension of 8 years' duration, treated with methyldopa and a diuretic, and rheumatoid arthritis for several years, treated with compound aspirin, phenacetin and caffeine tablets. There was no history of diabetes mellitus, glaucoma, ocular trauma, or other medical or ocular diseases. An ophthalmological examination 1½ years previously showed a corrected visual acuity of 20/25 in each eye, applanation tension of 22 mmHg OU and a cup/disc ratio of 0·25 in each eye.

Ophthalmological examination during the present illness revealed a corrected visual acuity of 20/30 OU. Applanation pressures were 42 mmHg OD and 10 mmHg OS. Slit-lamp examination of the anterior segment was normal in both eyes. Gonioscopic examination of the anterior chamber angle showed a grade III-IV open angle in both eyes, without recession or neovascularisation. However, the right eye showed blood present in Schlemm's canal (7.00 to 11.00 o'clock), and a haemorrhage localised to the trabecular meshwork from 7.00 to 8.00 o'clock (Fig. 1). On ophthalmoscopic examination cup/disc ratios of 0·45 OD and 0·15 OS were seen on stereoscopic examination at the slit-lamp. Outflow facilities were 0·14 OD and 0·21 OS. Goldmann kinetic perimetry was normal in both eyes. Systemic blood pressure was 190 mmHg systolic and 110 mmHg diastolic.

A complete blood count and sedimentation rate were normal. Antinuclear antibody and latex fixation tests were negative. Haemoglobin electrophoresis revealed an AS pattern. The 3-hour oral glucose tolerance test was abnormal: fasting blood sugar 117 mg/100 ml (6·5 mmol/l); at 1 hour 231 mg/100 ml (12·8 mmol/l); at 2 hours 166 mg/100 ml (9·2 mmol/l); at 3 hours 88 mg/100 ml (4·9 mmol/l).

The patient was treated with acetazolamide

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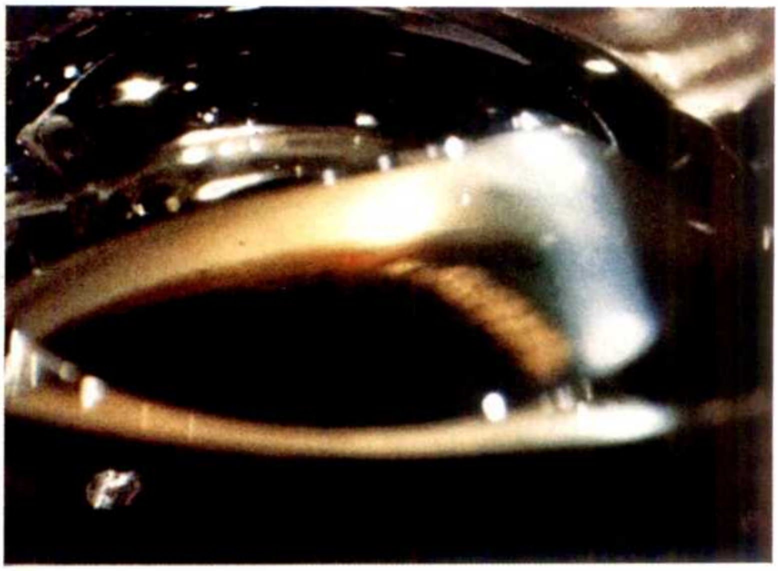

Fig. 1 *Goniophotograph of case 1 showing blood in the canal of Schlemm.*

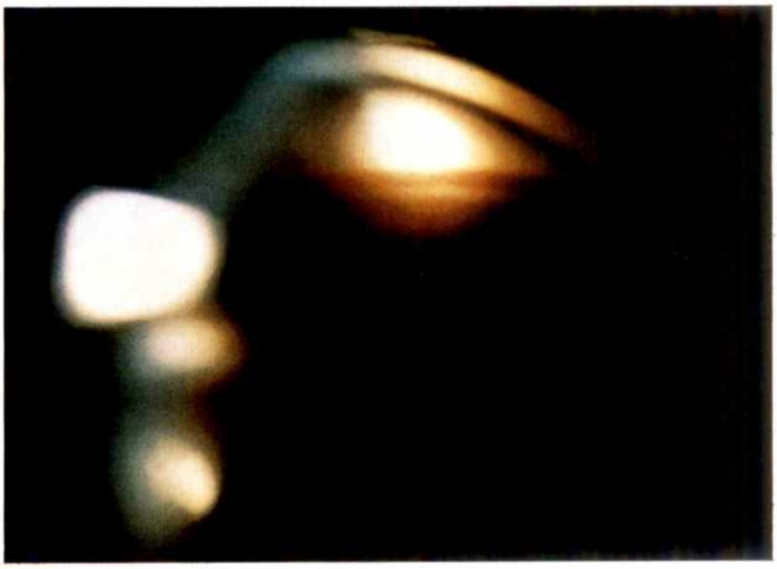

Fig. 2 *Goniophotograph of case 3 showing blood in the trabecular meshwork.*

250 mg orally 4 times a day and Epitrate (adrenaline acid tartrate) drops 2% OD twice a day. Over a 2-week period the trabecular haemorrhage and blood in Schlemm's canal resolved. The intraocular pressure remained normal after medication was discontinued and remained normal when the patient was last examined 18 months later.

CASE 2

A 9-year-old boy was struck in the left eye with a stick 24 hours before admission to hospital. He immediately developed a reduction in vision followed several hours later by pain in the eye and vomiting. Ocular examination showed the uncorrected visual acuity to be 20/20 OD and 20/200 OS. Applanation pressures were 10 mmHg OD and 40 mmHg OS. A superficial abrasion was present on the left upper eyelid. The left eye displayed moderate conjunctival hyperaemia and mild microcystic corneal epithelial oedema. The anterior chamber of the right eye was clear while the left eye had 3+ flare and cells (many erythrocytes). No gross hyphaema was seen at the slit-lamp. The pupillary reflex was brisk OD and sluggish OS. The vitreous and fundus were unremarkable. Gonioscopy of the left eye revealed blood in Schlemm's canal.

The patient was placed on bed rest, sedation, and acetazolamide 125 mg by mouth 4 times daily. Examination next day showed an uncorrected visual acuity in the left eye of 20/20 with intraocular tension 36 mmHg. Gonioscopy showed blood layered in the inferior portion of the anterior chamber angle and prominently in Schlemm's canal in the remainder of the angle. A sickle preparation was positive, and haemoglobin electrophoresis revealed an AS pattern (Hgb A 56%, Hgb S 44%). All other laboratory tests including complete blood count, urine analysis, sequential multiple analyser (SMA) 6 and 12 were normal. The haemorrhage cleared from the anterior chamber over the next 5 days with return of intraocular pressure to normal levels. The acetazolamide was discontinued without sequelae. The patient was asymptomatic when examined 24 months later.

CASE 3

A 23-year-old black man was struck in the right eye. He noticed a mild decrease in vision with pain in the eye. He was in excellent health otherwise. Ophthalmological evaluation showed a best visual acuity of 20/50 OD and 20/20 OS. The left eye was completely normal. Applanation pressures were 30 mmHg OD and 14 mmHg OS. The right eye had 2+ bulbar hyperaemia, clear cornea with very fine cellular deposits on the endothelium, 3+ aqueous flare, and cells (mostly erythrocytes). Gonioscopy revealed a grade 3 open angle OU with a dark red band of blood in the trabecular meshwork OD (Fig. 2). No peripheral anterior synechiae or recession of the anterior chamber angle were present. The pupillary reactions, lens, vitreous, and fundus were normal. Tonography at this time revealed a facility of outflow of 0·08 OD and 0·26 OS. The patient was put on acetazolamide 250 mg by mouth 4 times daily and prednisolone acetate 1% eye drops 4 times daily.

Haemoglobin electrophoresis revealed an AS pattern (Hgb A 55%, Hgb S 45%). All other laboratory studies, including complete blood count, urine analysis, SMA 6 and 12, and serum electrophoresis were within normal limits.

The blood cleared from Schlemm's canal 1 week after admission with a concomitant return of intraocular tension to 16 mmHg. The visual acuity returned to 20/20, but a repeat tonography showed a coefficient of outflow of 0·14 OD and 0·24 OS. Visual fields with tangent screen utilising a 3 mm white target at 1 m were normal in each eye. All medications were discontinued. The patient was discharged and lost to follow-up.

CASE 4

The patient was a 34-year-old black man who was punched in the left eye. When seen 2 days later the corrected visual acuity was 20/20 OD and 20/100 OS Intraocular pressure was 16 mmHg OD and 36 mmHg OS. The right eye was entirely normal. The left eye displayed 2+ bulbar hyperaemia and moderate microcystic corneal oedema. The cornea was cleared with topical glycerin. No keratic precipitates were present. The anterior chamber revealed 2+ aqueous flare and cells, many of which were erythrocytes. Gonioscopy showed a grade 3 open angle, both eyes, and in the left eye a dense column of dark red blood in Schlemm's canal. The pupillary reactions were brisk OD and sluggish OS. The lens, vitreous, and fundus appeared normal. The patient was placed on acetazolamide 250 mg by mouth 4 times daily and prednisolone acetate 1% drops 4 times daily. A complete laboratory examination and haemoglobin electrophoresis revealed AS pattern (Hgb A 59%, Hgb S 41%). The intraocular tension was unchanged over the next 24 hours, and consequently the patient was given oral glycerol 1·5 mg per kg. After 2 hours, the intraocular pressure was 22 mgHg in the left eye. Acetazolamide and glycerol were both required to control the intraocular tension for the ensuing 6 days. Examination at that time showed an intraocular pressure of 24 mmHg and blood in Schlemm's canal. Glycerol was discontinued. Visual fields utilising a tangent screen at 1 m with a 2 mm white target were full in both eyes. Tonography revealed a facility of outflow of 0·22 OD and 0·10 OS. During the next 10 days the blood in Schlemm's canal was gradually absorbed and the intraocular pressure was 16 mmHg. Tonography at that time was 0·20 OD and 0·20 OS. Ocular examination 18 months later was entirely within normal limits.

Discussion

The severity of symptoms in patients with sickle-cell trait depends on several factors any of which may increase the amount of sickling. These factors[13] are: the percentage of S haemoglobin, oxygen tension, pH, temperature, viscosity, vascular stasis, hyperkalaemia, increased carbon dioxide level, and presence of reducing substances. Thus, as Shapiro and Baum[12] observed, the consequence of small nontraumatic (case 1) or traumatic hyphaemas (cases 2, 3, 4) in a patient may be transient open-angle glaucoma due to the incarceration of sickled erythrocytes in the canal of Schlemm and trabecular meshwork.

An erythrocyte can pass through vessels smaller than its own diameter because of its ability to alter its own discoid shape. Thus the ease with which normal erythrocytes can negotiate the pathways through the trabecular meshwork, juxtacanalicular tissue, and into Schlemm's canal depends on their extreme plasticity and easy deformability. Inomata and associates[14] showed in the cynomolgus monkey that normal erythrocytes measuring approximately 6–7 µm in diameter could pass through the endothelial trabeculae and enter the vacuoles of endothelial cells through 2·5–3·5 µm pores by virtue of the erythrocyte's pliability. Erythrocytes then pass from the vacuoles into the canal of Schlemm through pores 1·0–1·8 µm in diameter. Erythrocytes can also pass through short pores 1·0 µm in diameter in the flat portion of the trabecular endothelium into the canal. In sickled erythrocytes[13] the haemoglobin becomes relatively insoluble and aggregates into long polymers possessing a tubelike structure 20–22 nm in diameter. Sickled erythrocytes are rigid and nonpliable and cannot pass through the trabecular meshwork. Reduced erythrocyte deformability has also been observed in thalassaemia spherocytosis and, recently, in diabetes mellitus.[15]

Presumably increased haemoglobin A_{Ic} (Hb A_{Ic}) formed by the glycosylation of haemoglobin causes an increased intracellular viscosity and a concomitant decreased erythrocyte deformability.[16] Goldberg[17] in his study of 3 patients with sickle-cell trait who sustained traumatic hyphaemas found that they had more sickling of erythrocytes in their aqueous than in their peripheral venous blood. In consonance with variations in haemoglobin S concentration in patients with sickle trait Goldberg[17] observed that a lower percentage of sickled erythrocytes was found in the aqueous of the patients with lower concentration of haemoglobin S. This observation is supported by studies on the inhibitory effect of deoxygenated normal haemoglobins (A or F) on the polymerisation of deoxygenated haemoglobin S.[13] In all our cases it would be difficult on the basis of clinical examination to determine the exact site(s) of entrapment of deformed erythrocytes.

Patient 1 was at first thought to have had a glaucomatocyclitic crisis because of the recurrent blurring of vision, painless elevation of intraocular pressure, a white eye, open angles, normal visual fields, and intraocular pressure between attacks.[18] The mild ocular hypertension (22mgHg OU) noted before the attacks and the cup/disc asymmetry are unusual in this entity, although a predilection for glaucomatocyclitic crisis in patients with primary open-angle glaucoma has been suggested.[19] The lack of evidence of anterior chamber inflammation in this patient on every examination, the persistence of blood in the trabecular meshwork or in Schlemm's canal, and the trabecular meshwork haemorrhage are all atypical for glaucomatocyclitic crisis and make this diagnosis untenable.

Boniuk and Burton[20] reported 2 cases of unilateral glaucoma associated with sickle cell retinopathy. They postulated that the glaucoma was secondary to neovascularisation and peripheral anterior synechiae within the chamber angle which developed as a sequel to intravascular sickling. None of our patients had sickle retinopathy, neovascularisation, or peripheral anterior synechiae.

Haemorrhage into the trabecular meshwork is an uncommon occurrence. Amsler and Verrey reported observing a haemorrhage in the anterior chamber angle following paracentesis in Fuchs's heterochromic iridocyclitis and considered it to be characteristic.[21] Haemorrhage from Schlemm's canal has been reported to have been induced by gonioscopy in these patients[22,23] and in a few normal and glaucomatous eyes.[24] However, none of our patients had heterochromia iridis, as is typically seen in Fuchs's iridocyclitis.[25,26] Trabecular haemorrhage has also been observed in severe iridocyclitis,[27] but none of our patients had evidence of severe ocular inflammation.

The spontaneous reflux of blood into Schlemm's canal may occasionally be seen in conditions that produce ocular hypotony or raised episcleral venous pressure.[28] Increased episcleral venous pressure may be produced by gonioscopy and by inflating a blood pressure cuff about the neck. Either manoeuvre may produce obstruction of blood flow through the jugular veins. Sickle-cell disease, hypertension, rheumatoid arthritis, and diabetes mellitus are all associated with small-vessel disease, which may be associated with episcleral venous obstruction and stasis and lead to sickling of blood that has spontaneously refluxed into Schlemm's canal. Cogan and coworkers reported that in diabetes mellitus patients may have an elevated serum viscosity.[29] Coupled with an increased intracellular viscosity due to glycosylation and decreased erythrocyte deformability,[15,16] these may also predispose to venous stasis and sickling.

The treatment of what may hitherto have been described as 'insignificant' hyphaemas in blacks must be re-evaluated. All blacks with hyphaemas should have sickle screening tests and haemoglobin electrophoresis. Because of the effects of increased intraocular pressure in reducing perfusion to the retina and optic nerve in patients with sickle trait, extreme care must be undertaken in monitoring the intraocular pressure.[7,9] The ophthalmologist must be judicious in the use of carbonic anhydrase inhibitors and osmotic therapy. Increased serum tonicity after diuretic and osmotic therapy in association with vascular stasis coincident with increased intraocular pressure may precipitate vascular occlusions in patients with sickle-cell trait.[11] And, as Goldberg[17 30] has suggested, early anterior chamber paracentesis may be the most efficacious method of removing sickled erythrocytes from the anterior chamber.

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Sickle cell trait and diabetic retinopathy

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SUMMARY The presence of sickle cell trait and the prevalence and severity of retinopathy were assessed in 124 Negro diabetics. Sickle cell trait had no adverse effect on diabetic retinopathy.

Retinal neovascularisation occurs infrequently in sickle cell anaemia (Condon and Serjeant, 1972a) but slightly more commonly in other haemoglobinopathies such as sickle cell haemoglobin C disease (Condon and Serjeant, 1972b) and sickle cell thalassaemia (Condon and Serjeant, 1972c). It has been reported in 2 patients with sickle cell trait, 1 of whom had diabetes mellitus (Goldberg and Acacio, 1973). We wondered if sickle cell trait might aggravate diabetic retinopathy by inducing sickling in pre-existing areas of focal ischaemia and hypoxia in the retina. A study was therefore performed to determine whether the presence of sickle cell trait affected the prevalence or severity of diabetic retinopathy, especially the development of neovascularisation.

Patients and methods

We could identify 446 West Indian diabetics attending the clinic with the help of a computerised record system. From this group 13 of 16 Negro diabetics with known background retinopathy (2 had died and 1 was untraced) were studied, together with a random selection of those not known to have retinopathy with the longest clinic attendances. No case of retinal neovascularisation had been identified in all these Negro diabetics prior to this study.

Corrected visual acuity and fundal examination after pupillary dilatation was performed by one of us (J.P.), who was unaware of the results of haemoglobin electrophoresis. Statistical significance was assessed by the chi-square test with Yates's correction.

Results

There was no significant difference between the proportion of diabetics with sickle trait in those with neovascularisation or background retinopathy, or among those without retinopathy. Average age and duration of diabetes was the same in all 3 groups (Table 1).

Table 1 *Details of patients*

Group		*Haemoglobin electrophoresis*	
		Sickle trait	*Normal*
Neovascularisation	Number	4	23
	Average age (years)	52·0 (40–61)	57·3 (36–76)
	Average duration of diabetes (years)	5·3 (2–12)	9·8 (1–20)
Background retinopathy	Number	8	41
	Age	53·3 (46–63)	54·1 (36–76)
	Duration of diabetes	9·6 (3–20)	9·3 (1–18)
No retinopathy	Number	6	42
	Age	57·3 (40–70)	48·4 (37–72)
	Duration of diabetes	5·2 (2–6)	5·8 (1–21)

Mean age and duration of diabetes shown, with range in parentheses.

Three of the 4 patients with sickle trait had developed new vessels within 3 years of diagnosis of diabetes compared with 4 of 23 with normal haemoglobin electrophoresis, but the difference was not significant ($P > 0{\cdot}20$). There was no significant difference in visual acuity between the groups. There were 10 eyes with visual acuity equal to or less than 6/60 in the non-sickle neovascularisation group but none in those with sickle trait. One diabetic was found to have sickle cell haemoglobin C disease and had minimal background retinopathy after 15 years of diabetes.

Discussion

The results seem to exclude the possibility that sickle cell trait might aggravate diabetic retinopathy. The prevalence of sickle cell trait was not increased in diabetics with background or proliferative retinopathy and there was no diminution in visual acuity in those with sickle trait. We conclude that sickle

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cell trait has no influence on the presence or severity of diabetic retinopathy.

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Ocular findings in sickle cell-haemoglobin O Arab disease

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SUMMARY The ocular findings in 2 patients with sickle cell-haemoglobin O Arab disease are described. One patient had proliferative sickle cell retinopathy with extensive autoinfarction of lesions. Sickle cell-haemoglobin O Arab disease must be added to the list of conditions that may be associated with proliferative sickle cell retinopathy.

Sickle cell-haemoglobin O Arab (SO Arab) disease results from the inheritance of 2 abnormal β chains, and is a rare condition resembling sickle cell-haemoglobin C (SC) disease on routine haemoglobin electrophoresis at alkaline pH. Previous observations suggested that the clinical and haematological severity was intermediate between that of SC disease and homozygous sickle cell (SS) disease (Milner *et al.*, 1970). In view of the high prevalence of proliferative sickle cell retinopathy in SC disease it was of interest to report the ocular lesions occurring in 2 patients with SO Arab disease.

Patients and methods

Approximately 2000 patients with different genotypes of sickle cell disease attend the sickle cell clinics at the University Hospital of the West Indies. Of these, 4 patients have been identified as SO Arab disease (Milner *et al.*, 1970), and the present 2 patients represent cases 3 and 4 in that report. The diagnosis of SO Arab disease was based on criteria described by Milner *et al.* (1970). Mean steady state haematological findings in the 2 patients are summarised in Table 1.

CASE 1

A 15-year-old black female had been followed up in the Sickle Cell Clinic for 3 years with a history of intermittent joint pains and chronic leg ulceration. She had no eye complaints, and examination showed a visual acuity of 6/6 in both eyes. Abnormalities of conjunctival vessels typical of sickle cell disease (Paton, 1961) were present, the ocular media were clear, and the optic discs and maculae normal. Peripheal venous tortuosity and arteriolar narrowing with some peripheral whiteness without pressure was present in localised quadrants (Fig. 1). A brown mottling of the peripheral retina was noted in the inferotemporal left quadrant. There was no evidence of proliferative sickle retinopathy. The patient subsequently emigrated and was lost to follow-up.

CASE 2

A 52-year-old black female has been followed up in the clinic for 10 years with a history of intermittent joint pains, leg ulceration, and gallstones. There was a history of sudden visual loss in the right eye years ago with subsequent improvement of acuity, which did not return to normal, and then vision gradually deteriorated. On examination in April 1973 visual acuity was 3/60 in the right eye and 6/12 in the left eye. Abnormalities of conjunctival vessels were present, the ocular media were clear,

Table 1 *Steady-state haematological findings in the 2 patients*

Patient no.	*Hb (g/dl)*	*PCV (g/dl)*	*MCHC (g/dl)*	*RBC* ($\times 10^{12}$/*l*)	*MCV (fl)*	*MCH (pg)*	*Retics (%)*	*ISC (%)*	*Total bilirubin (mg/dl)*	*Serum Fe (μg/dl)*
1	8·8	0·26	34	3·12	82	28	2·0	4·2	1·2	92
2	8·4	0·27	31	3·46	76	24	6·6	3·0	1·0	74

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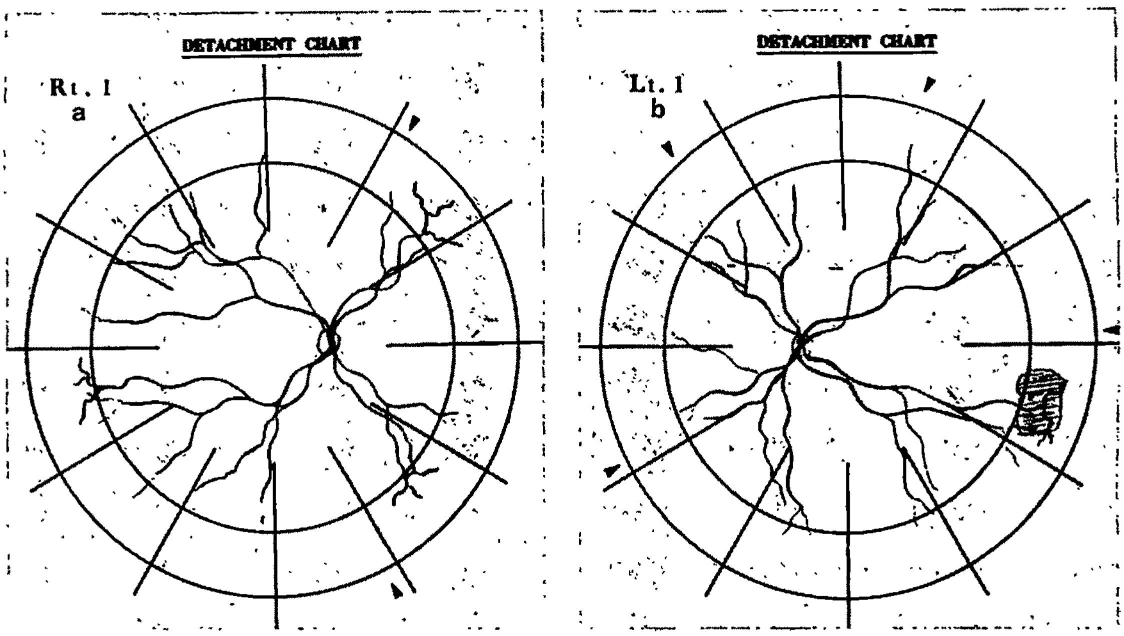

Fig. 1 *Retinal drawing of findings in patient 1.* (a) *Right eye—peripheral whitening between 1 o'clock and 5 o'clock (depicted by arrow heads).* (b) *Left eye—peripheral whitening between 8 o'clock and 11 o'clock and between 1 o'clock and 3 o'clock. Shaded area—Pigmented chorioretinal lesion*

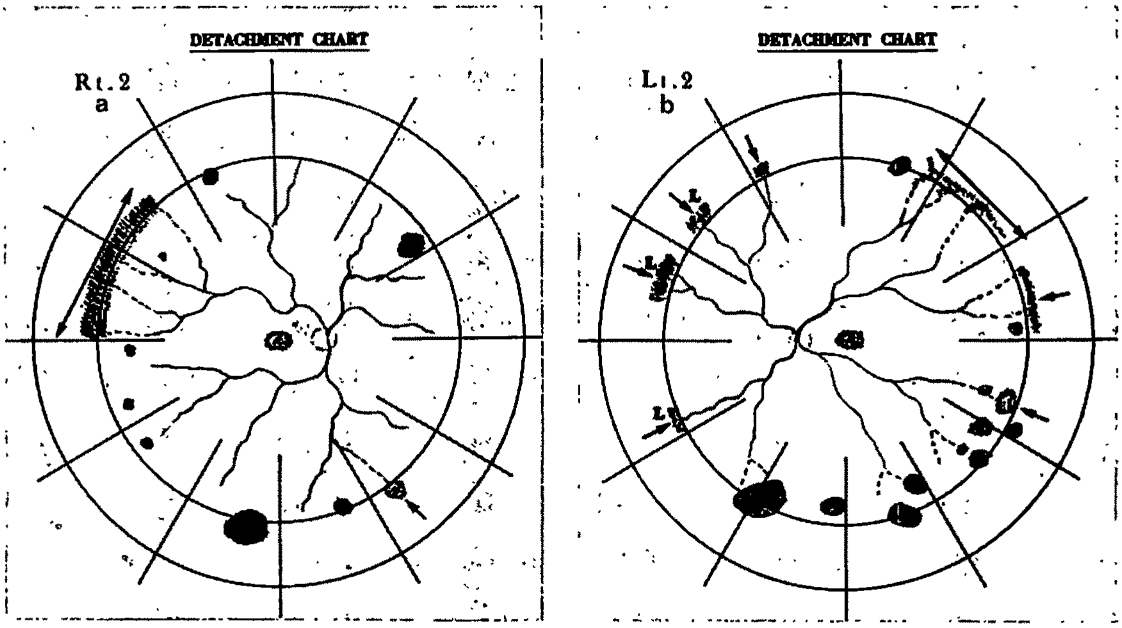

Fig. 2 *Retinal drawing of findings in patient 2.* (a) *Right eye.* (b) *Left eye. Shaded areas indicate pigmented chorioretinal lesions. Dotted lines indicate occluded arterioles. Arrows depict occluded proliferative retinopathy and arrows with L indicate leaking proliferative retinopathy. Macular drusen*

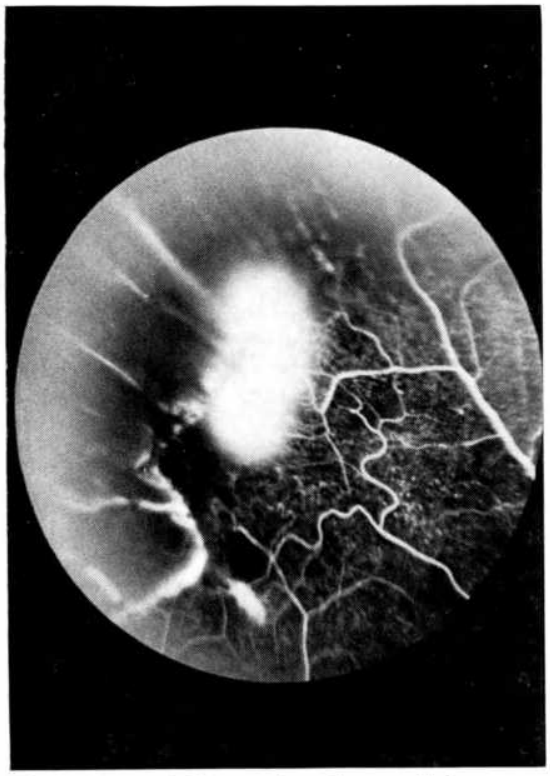

Fig. 3 *Patient 2. Fluorescein angiogram of left superonasal periphery with leaking proliferative sickle cell retinopathy lesion*

and both fundi were easily seen. Both optic discs showed physiological cupping. A mottled pigment epithelial change affected both maculae, the right more than the left, but there were no signs of macular oedema. Occluded retinal arterioles occupied the complete circumference of both eyes and extended posteriorly to the equator in places. Occluded proliferative retinopathy was noted in the superotemporal and inferonasal peripheral retina of the right eye (Fig. 2a) and in the superotemporal region of the left eye (Fig. 2b). Three leaking proliferative lesions were seen in the nasal region of the left eye. Multiple areas of pigmentary disturbance (sunburst spots) occurred in both eyes and a posterior vitreous detachment in the right eye. Fluorescein angiography confirmed leaking proliferative sickle cell retinopathy lesions at the junction of vascular and ischaemic retina (Fig. 3).

Re-examination of the patient in February 1977 and July 1978 showed little change. The vision had deteriorated to counting fingers in the right eye and to 6/18 in the left, the macular pigment epithelial changes having progressed. Black sunburst spots increased in number in both eyes. The leakage from proliferative lesions in the left eye had diminished by autoinfarction to about 50% of that observed in 1973.

Discussion

The retinal vascular changes that occur in other forms of sickle cell disease may also be found in SO Arab disease. The first patient showed mild changes of peripheral venous tortuosity and arteriolar narrowing comparable to the findings in many patients with SS disease at this age. In the second patient moderately severe proliferative sickle cell retinopathy was undergoing autoinfarction. The gradual deterioration of visual acuity in this patient may have been caused by the progressive macular changes, and the history of sudden but transient visual loss may have represented a vitreous haemorrhage.

Although uncommon, sickle cell-haemoglobin O Arab disease must be added to the list of sickle cell conditions associated with proliferative retinopathy and possible visual impairment.

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Ocular findings in a case of haemoglobin H disease

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SUMMARY A case is reported of a patient with known haemoglobin H disease who was found to have angioid streaks and retinal detachment. Angioid streaks have not previously been reported in cases of α-thalassaemia, and the question whether this is a chance association or otherwise is discussed.

Angioid streaks, first described by Doyne (1889), appear on ophthalmoscopic examination as reddish brown or greyish striations, which usually form a network around the optic disc and radiate outwards. They may be single or multiple, are predominantly bilateral, but usually asymmetrical in the 2 eyes. Angioid streaks have been reported in association with certain systemic diseases, notably pseudoxanthoma elasticum (PXE) and osteitis deformans (Paget's disease) (Paton, 1972). They have also been reported in association with abnormal haemoglobins, particularly homozygous sickle cell anaemia (Condon and Serjeant, 1976). Angioid streaks do not appear to have been recorded in association with any variety of α-thalassaemia.

This report describes a patient with haemoglobin H disease (HbH), an α-thalassaemia, who was found to have angioid streaks and a retinal detachment.

Case report

A 44-year-old Greek Cypriot was diagnosed as having HbH in 1968. Recurrent leg ulceration had led to several hospital admissions, the last being in 1976, when initial ophthalmoscopic examination was undertaken. Since childhood the patient had had a squint and poor vision in the left eye, but gave no history of trauma to either eye. He smoked between 20 and 40 cigarettes per day. The family history was not significant. His 3 children did not have HbH. On examination there were 3 ulcers on the right leg and some scarring over the left leg. Mild clubbing of the fingers and toes was also present. Liver and spleen were not enlarged. There were no dermatological stigmata of pseudoxanthoma elasticum, and skin biopsy was normal.

Examination of the eye revealed moderate scleral icterus, a left divergent squint, and visual acuities of 6/5 right eye and 2/60 left eye. The fundus of the right eye showed an angioid streak running from the optic disc towards the macula. The divergent left eye had a long-standing inferior half retinal detachment, in which only a small segment of flat retina was detected. The left fundus also showed considerable vitreous disorganisation and peripheral retinal degenerative changes, but no angioid streaks were seen. The peripheral retinal vessels in the left eye appeared normal in the upper half of the fundus, while those in the lower half appeared attenuated. No proliferative vascular lesions were noted.

Fluorescein angiography of the retina demonstrated the typical late hyperfluorescence of angioid streaks in the right eye. In addition to the angioid streak seen at ophthalmoscopy, fluorescein angiography also revealed 3 small streaks radiating superiorly from the upper border of the optic disc (Fig. 1).

Laboratory results were as follows: haemoglobin 9·5 g/dl, reticulocyte count 3·8 %, normal white blood cell morphology, but red cells showed marked anisocytosis, poikilocytosis, target cells, and gross hypochromasia. Supravital staining with brilliant cresyl blue showed that all red cells contained numerous H bodies. HbH was confirmed on electrophoresis and comprised 23·5 % of total haemoglobin, while carboxyhaemoglobin comprised 7·4 % of total haemoglobin. Plasma bilirubin was raised at 40 μmol/l.

Follow-up in May 1979 did not reveal any progression of the angioid streaks or change in visual acuity.

Discussion

The above case records the association of angioid streaks in HbH, an α-thalassaemia. Though they

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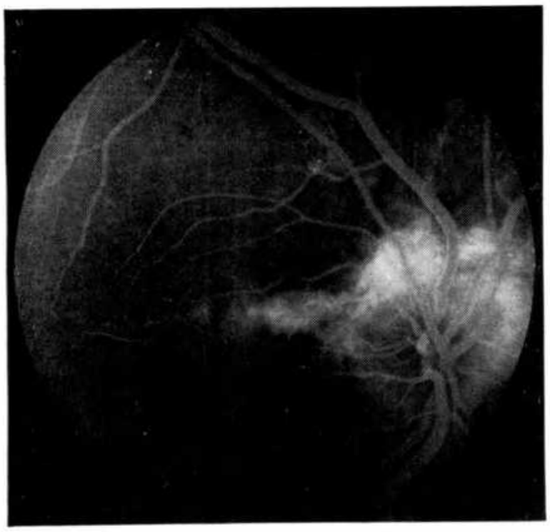

Fig. 1 *Fluorescein angiogram of the right retina showing the typical hyperfluorescence of angioid streaks radiating from the optic disc (on the right) to the macula (on the left), and from the optic disc upwards.*

were detected in only one eye, their presence in the other eye cannot be excluded, since adequate examination was hindered by the retinal detachment. Detachment of the retina has been observed in association with angioid streaks, often beginning at the site where several streaks intersect (Archer and Logan, 1977). However, in this patient no angioid streaks were evident in the left eye. Retinal detachment has been seen in sickle cell haemoglobin C disease (HbSC) (Goldberg, 1971), almost invariably in association with a proliferative vascular retinopathy and the pathognomonic 'sea-fan' lesion. Neither the sea-fan lesion nor proliferative vascular changes were seen in this patient, and though one may postulate other mechanisms—for example, retinal ischaemia—the cause of the retinal detachment is not evident. Other nonophthalmological features of this case are the absence of splenomegaly and the presence of leg ulcers. The latter have been described and discussed elsewhere (Daneshmend and Peachey, 1978).

Haemoglobinopathies in which ocular involvement has been reported include homozygous sickle cell anaemia (HbSS) (Goodman *et al.*, 1957; Condon and Serjeant, 1976), sickle cell trait (HbAS) (Gerde, 1974; Radius and Finkelstein, 1976), sickle cell haemoglobin C disease (HbSC) (Goldberg, 1971; Condon and Serjeant, 1972a; Ryan, 1974), sickle cell β-thalassaemia (HbS β-thal) (Goldberg *et al.*, 1971; Condon and Serjeant, 1972b), and haemoglobin C trait (HbAC) (Moschandreau *et al.*, 1974).

Angioid streaks have been noted in association with 4 of the above disorders, namely, HbSS (Geeraets and Guerry, 1960; Condon and Serjeant, 1976), HbAS (Gerde, 1974), HbSC (Condon and Serjeant, 1972a; Nagpal *et al.*, 1976), and HbS β-thalassaemia (Goldberg *et al.*, 1971; Nagpal *et al.*, 1976). Their incidence in association with haemoglobinopathies as a whole has been estimated at 0·94% (Paton, 1972). However, the incidence of angioid streaks in association with any particular haemoglobinopathy remains to be clarified. For example, in HbSS Geeraets and Guerry (1960) gave an incidence of 6%, but Nagpal *et al.* (1976) found angioid streaks in less than 2%, whereas Condon and Serjeant (1976) found them in more than 20% of their elderly group of patients.

Only 1 case has been reported of angioid streaks in HbAS (Gerde, 1974). Similarly angioid streaks have been found in only 2 cases each of HbS β-thalassaemia (Goldberg *et al.*, 1971; Nagpal *et al.*, 1976) and HbSC (Condon and Serjeant, 1972a; Nagpal *et al.*, 1976). Angioid streaks have not been reported in pure α-thalassaemia or any variety of β-thalassaemia.

There is a profusion of unsatisfactory theories to explain the presence of angioid streaks in haemoglobinopathies. An elastic tissue defect was suggested by Geeraets and Guerry (1960), but routine skin biopsies show no evidence of this. Paton (1959) thought that vascular obstruction affecting the choriocapillary circulation may be a causative factor. However, 3 patients who developed posterior ciliary vessel obstruction and subsequent segmental chorioretinal atrophies did not develop angioid streaks (Condon *et al.*, 1973). More recently Paton (1972) has favoured chronic haemolysis leading to iron deposition in Bruch's membrane as a cause of degeneration and angioid streak formation. But patients with haemochromatosis or haemosiderosis have not been noted to have angioid streaks. The association of angioid streaks with a dozen other disorders (Hogan and Heaton, 1973) has not helped to clarify their pathogenesis. Thalassaemias, including HbH, are relatively common in Thailand, but Wasi (personal communication) has not so far noted angioid streaks. Therefore it seems probable that they are an unusually rare finding in HbH.

The importance of angioid streaks as markers of more significant underlying disease has been amply stressed in the past. In view of the secondary phenomena associated with them, namely, retinal haemorrhages and macular lesions (Archer and Logan, 1977), it is suggested that patients with a haemoglobinopathy have fundal examinations as part of their medical care. These observations may uncover the enigmatic aetiology of angioid streaks in diseases without demonstrable connective tissue abnormalities.

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Ocular involvement in scleroderma

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SUMMARY Thirty-eight patients with scleroderma (progressive systemic sclerosis) without renal failure were subjected to detailed clinical ophthalmic assessment. Abnormalities were frequent. However, many of these, including lens opacities, vitreous frosting, and arteriosclerotic changes, were considered to be age-related, and there were various incidental changes. Posterior subcapsular lens opacities in one patient were probably corticosteroid-induced. Changes related to scleroderma included eyelid abnormalities (stiffness or tightness in 11, telangiectasia in 8), deficient tear secretion (14 cases), and conjunctival abnormalities (injection 19 cases, vascular sludging 27 cases). Iris light reflux (6 cases) was possibly related to scleroderma. The changes related to scleroderma occurred in the 3 types classified according to the extent of skin involvement.

Scleroderma with systemic involvement (progressive systemic sclerosis) is an unusual but not rare disease. Its clinical and laboratory features have been analysed in some detail in numerous papers, reviewed in a recent monograph.[1] Ocular involvement in scleroderma is widely recognised,[2-4] but the nature, frequency, and relevance of the ocular changes remain the subject of some uncertainty. The occurrence of severe fundal changes in acute terminal renal failure associated with scleroderma has been well documented.[5] The purpose of this paper is to explore the clinically significant ocular features in a group of patients affected by scleroderma of different degrees of severity but not in renal failure.

Patients and methods

The study was conducted on 38 outpatients with scleroderma, comprising 31 women and 7 men, ranging in age from 22 to 76 years, median age 60 years. With the exception of one Arabic Lebanese woman all were of Caucasian stock. They were classified according to the extent of the skin sclerosis as proposed by Barnett and Coventry[6] as follows: type 1, skin changes of fingers only (17 patients); type 2, skin changes beyond fingers but more marked in limbs and face (16 patients); type 3, diffuse changes involving trunk (5 patients). Types 1 and 2 are sometimes combined as 'acrosclerosis'. Almost all had evidence of some systemic disorder either clinically or on tests.

The patients were subjected to a careful ophthalmic assessment, including applanation tonometry, biomicroscopy of the anterior segment and vitreous, and examination of the ocular fundus by direct and indirect ophthalmoscopy after the instillation of mydriatic drops.

We sought sludging or segmentation of the blood columns in conjunctival vessels mainly of venular calibre, using biomicroscopic magnification. The appearance of the vitreous fibrils was assessed minutely by biomicroscopy and contact lens examination, with particular reference to thickening, nodularity, or cellular deposits in the vitreous framework. Stiffness and loss of elasticity of eyelid skin was assessed subjectively. Lacrimal function was assessed by examination of the cornea and conjunctiva after the instillation of Rose-Bengal drops and by a Schirmer test,[7] wetting of the filter paper strip less than 10 mm after 5 minutes being taken as indicating reduced tear secretion.

Results

Eyelid changes. Tightness of the skin of the eyelids was found mainly in type 2 cases. Associated shortening of the interpalpebral fissure as reported by Kirkham[3] was found in only 1 patient. Telangiectases of the eyelid skin were generally tiny, seldom exceeding 1 mm in diameter, and were best detected under biomicroscopic magnification.

Lacrimal function. Deficient tear secretion was

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found in a proportion of patients of all 3 types. As some patients with disturbed lacrimal function show normal results at one visit and abnormal results at another, suggesting intrinsic variation or perhaps some influence of environmental conditions, the incidence of tear defects is probably underestimated in this study.

Conjunctival changes. These comprised vascular congestion, telangiectasia and varicosities of conjunctival vessels, intravascular sludging, and loss of fine vessels, all of which occurred in all 3 types. The varicose vessels were found mainly in relation to the corneoscleral limbus. Both varicosities and sludging were greatly reduced by the instillation of a vasoconstrictor solution (phenylephrine HCl 10%) used to facilitate mydriasis.

Lens opacities. Lens opacities mainly of the nuclear or cuneiform type occurred in several patients.

Vitreous changes. Vitreous syneresis and collapse were present in the expected proportion for this age group. Particular attention was paid to the appearance of fine nodularity or encrusting of vitreous fibrils ('vitreous frosting') as a possible index of low-grade intraocular cellular inflammation. It was observed in about one-third of the patients.

Fundus abnormalities. Retinal arteriosclerosis (indicated by variations in calibre, tortuosity or shortening, wall changes in retinal arteries, and arteriovenous crossing changes) was found in several patients of each type. Colloid bodies (drusen) distributed irregularly about the posterior pole were present in all disease types but were not present in any patients below the age of 63 years. The single instance of peripheral schisis of the retina was seen in 1 eye of a 63-year-old patient with retinal arteriosclerosis, and is to be regarded as of senile rather than of dystrophic significance. Cystoid retinal change observed in 1 eye of 1 patient was of uncertain pathogenesis, but might represent a previous localised vascular or inflammatory disorder. (No history of trauma was elicited.) A retinal branch vein occlusion seen in 1 patient was associated with retinal arterial sclerosis with constriction of the affected venous branch due to sclerosis of the adjacent arterial adventitial sheath.

Iris reflux. Spotty areas of transillumination in all zones of the iris caused by localised defects in the iris pigment epithelium were seen in several patients, mainly with lightly pigmented grey or blue irides.

Intraocular pressure. In both patients with raised intraocular pressure the condition was not associated with optic disc changes or visual field loss, and occurred in the presence of a normally open anterior chamber angle.

Discussion

The retinal changes in scleroderma with advanced renal failure have been described[5] but are not applicable to the patients in this study. Other writers have described the following changes in scleroderma without renal failure: eyelid sclerosis and telangiectasis,[2 4] conjunctival congestion or oedema,[2] defects of lacrimal secretion,[2 3] iris atrophy, and retinal exudates.[4] However, no systematic study of ocular changes in a large number of patients as presented has been reported previously.

In considering the large variety of ocular abnormalities revealed in this study some separation of the changes may be made provisionally into those related to the age of the individual, those due to previous or current treatment, and those due to scleroderma or associated disease.

Presumed age-related abnormalities. Certain of the abnormalities—cuneiform and nuclear lens opacities, vitreous frosting (the 'senile peppering' of Koby[6]), colloid bodies of the posterior pole, and retinal arteriosclerosis, are age-related, and their incidence would not appear to differ markedly from that in the general population. Raised intraocular pressure, found in 2 of the 38 patients, is consistent with a spontaneous partial manifestation of chronic simple glaucoma in a middle-aged and elderly population. One of these patients had been on systemic steroid therapy, but steroid provocative testing failed to support the possibility of a steroid-induced glaucoma.

Changes presumably related to treatment. Posterior subcapsular lens opacities were noted in 1 patient who had been treated with systemic corticosteroids for many years. Her lenses were later extracted with a good visual result.

Changes probably related to scleroderma. The following changes, not explicable by age or treatment, were probably related to scleroderma: eyelid changes, conjunctival changes, lacrimal disturbance. The iris changes in the absence of other known causative factors (diabetes, moderate or high myopia, pseudoexfoliation of the lens capsule, and pigmentary glaucoma) are possibly related to scleroderma. The eyelid features (tightness, telangiectasia, and blepharitis) were more common in types 2 and 3, in which the skin changes were more extensive.

Relationship of changes to other manifestations of scleroderma. Two of the most prominent features of scleroderma are alterations in connective tissue and vascular changes. The stiffness of the eyelid skin is in accordance with other connective tissue involvement. The telangiectasia of the eyelids and conjunctiva is probably related to similar changes seen elsewhere, particularly in the face and hands. The dilatation of venules and intravascular sludging in the conjunctivae are similar to changes described in the nailbed capillaries.[9] It is of interest that the vascular changes are not necessarily greatest in the location of the most marked connective tissue changes, which indicates that these 2 prominent features do not necessarily run parallel in severity. The pathological basis of the decreased lacrimal secretion is not clear, but in the absence of other features of Sjögren's syndrome, except in 1 patient would seem to be specifically related to scleroderma. As is the case with other systemic disturbances in scleroderma,[10] the associated eye changes occur in all 3 types.

Conclusion

Ocular changes which appear to be specifically related to scleroderma include: telangiectasia and dermal sclerosis of the eyelids; a tear defect of varying severity; injection, telangiectasia, and sludging of the blood column in conjunctival vessels; possibly punctate defects of the iris pigment epithelium. Posterior subcapsular lens opacities in 1 case were attributed to long-term systemic steroid therapy.

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Diagnosis and management of a wooden orbital foreign body: case report

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SUMMARY The case history of a patient with a retained wooden orbital foreign body is presented. The report illustrates the diagnostic limitations of orbital CAT scanning and ultrasonography. Systemic corticosteroid therapy facilitated the localisation and surgical removal of the foreign body.

A wooden orbital foreign body may present considerable diagnostic difficulty, as illustrated by the reports of Von Márton (1969), Ferguson (1970), and Legras and Lecoq (1970). The radiolucent nature of the foreign material prevents localisation by routine orbital radiography, but with the advent of orbital CAT scanning and ultrasonography the likelihood of identification should be increased.

The report which follows demonstrates the diagnostic and therapeutic problems still presented by such cases despite orbital investigations by CAT and ultrasonography.

Case report

A 46-year-old man attended the local casualty department after sustaining an injury to his left eye. While pruning a tree he had received a glancing blow from the terminal twig of a branch. The casualty officer diagnosed a conjunctival abrasion, prescribed antibiotic ointment, and advised the patient to seek specialist advice if the eye did not settle.

During the next 3 days the patient's left eye became increasingly painful and swollen. Four days after the injury he attended the ophthalmology clinic at Ninewells Hospital.

On examination the unaided visual acuity of the left eye was found to be 6/9. There was marked chemosis of the lower bulbar conjunctiva with prolapse between the eyelids. A bulbar conjunctival laceration approximately 10 mm in length was noted (Fig. 1). The cornea was clear, anterior chamber quiet, pupil normally reactive, and fundus normal on direct ophthalmoscopy.

The patient was admitted to the ophthalmology department and systemic and topical antibiotic therapy begun. Orbital *x*-rays did not reveal any evidence of a radioopaque foreign body or fracture. The conjunctival wound was explored, cleaned, and repaired under general anaesthesia.

Postoperatively the conjunctival chemosis did not resolve and the ocular movements of the left eye were noted to be limited. Repeated conjunctival swabs were sterile, microscopy of conjunctival scrapings did not reveal any micro-organisms or fungal elements, and culture on Sabouraud's agar was negative.

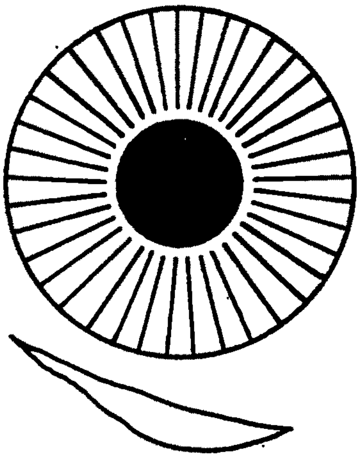

Fig. 1 *Diagram of left eye showing position and extent of the conjunctival laceration*

The conjunctiva remained prolapsed, and 7 days after the surgical repair a mattress lid suture was inserted under local anaesthesia to provide protection and tamponade. The chemosis then subsided considerably and the patient was discharged from

Correspondence to Mr Macrae.

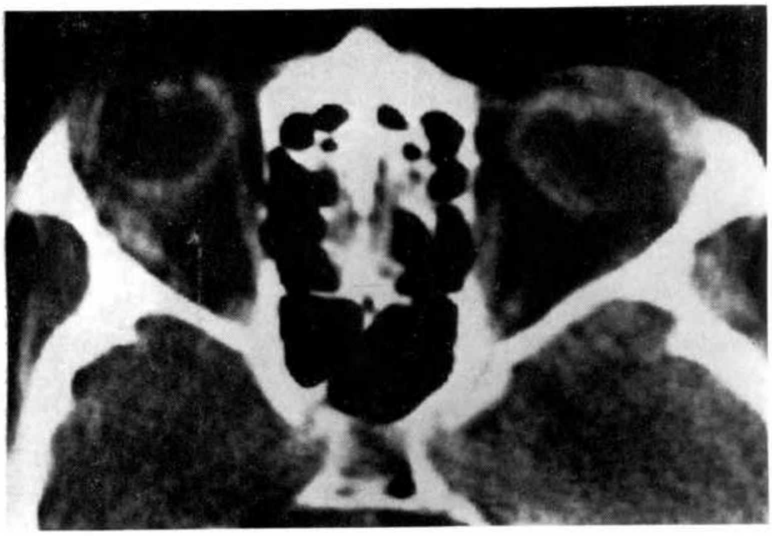

Fig. 2 *Orbital CAT scan after intravenous injection of contrast medium. An area of increased density is apparent posterolaterally in the left orbit in association with the lateral rectus muscle*

hospital with the lid suture in situ. Two weeks later the suture was removed and the conjunctival chemosis reappeared, particularly at the nasal side, where a pedunculated lesion developed. This lesion was excised under local anaesthesia and subjected to histological examination, which indicated a mixed acute and chronic inflammatory cellular infiltration. Special staining techniques did not reveal any microorganisms or fungi.

Diplopia then became a prominent symptom. The patient developed a left convergent strabismus of 40 prism dioptres in the primary position, with limitation of all ocular movements of the left eye, especially abduction, which was almost absent.

An orbital CAT scan was performed. This showed an area of increased density corresponding to the left lateral rectus muscle. Slight enhancement followed the injection of contrast medium, raising the possibility of a granulomatous lesion. No positive evidence of an orbital foreign body was detected (Fig. 2).

Similarly, orbital ultrasonography did not provide any definite evidence of a retained orbital foreign body.

Fundus examination of the left eye was performed by binocular indirect ophthalmoscopy. This revealed a lesion identical in appearance to a shallow radial scleral buckle, extending from the inferior temporal periphery to the posterior pole below the macular area (Fig. 3). This finding was consistent with external pressure on the sclera, possibly due to a localised granulomatous lesion or a foreign body lying in contact with the globe.

The chemosis of the lower bulbar conjunctiva persisted.

After the conjunctival biopsy and orbital CAT scan, both of which suggested a granulomatous pathology, and in the absence of an infective aetiology, it was decided to initiate a trial of corticosteroid therapy. The patient received oral prednisolone, 40 mg daily, and topical betamethasone to the left eye, in addition to antibiotic therapy.

The conjunctival chemosis rapidly subsided, the range of movement of the left eye increased, and the fundus lesion became shallower. The visual acuity of the left eye remained 6/9. The dose of oral prednisolone was retained at the level of 40 mg per day for 2 weeks, then gradually reduced to 20 mg daily over a further 4-week period. By this time the

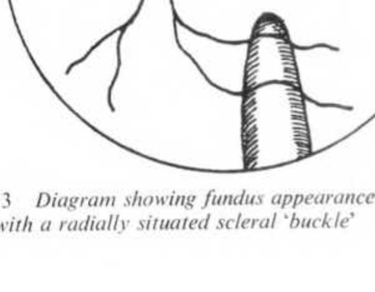

Fig. 3 *Diagram showing fundus appearance of left eye with a radially situated scleral 'buckle'*

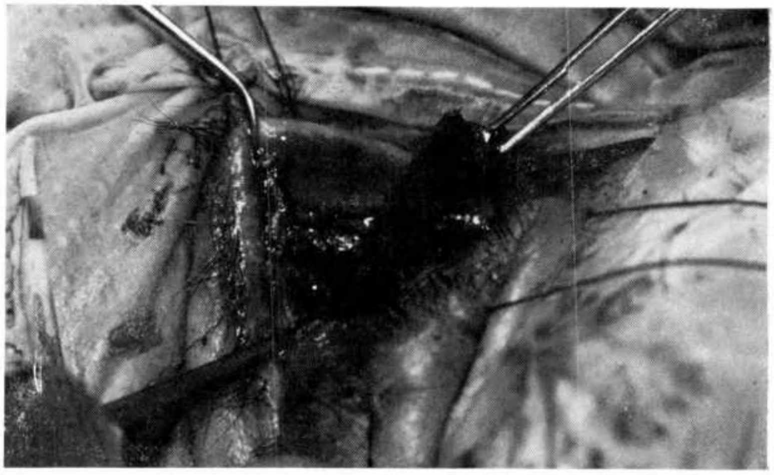

Fig. 4 *Removal of the wooden foreign body from the left orbit. The eye is rotated upwards and the lower eyelid retracted with a squint hook*

chemosis had almost resolved and the fundus appearance become normal.

With the subsidence of the tissue swelling it was then possible to palpate, through the left lower eyelid with the eye in upgaze, a circumscribed hard mass situated on the surface of the globe just lateral to the position of the inferior rectus muscle.

The patient underwent exploratory surgery under general anaesthesia. The operative findings were dramatic. Approximately 15 mm from the limbus at the lateral border of the inferior rectus muscle a hard circular mass was found in contact with the sclera and encapsulated by fibrous tissue. The mass was grasped with forceps and withdrawn to reveal its identity as the broken end of a wooden twig measuring 23×4 mm (Figs. 4 and 5). The wound was sutured and a subconjunctival injection of gentamicin given. Postoperative recovery was uneventful and the patient was discharged from hospital 2 days after surgery. The systemic corticosteroid therapy was gradually reduced and was discontinued 10 days postoperatively.

The residual conjunctival chemosis and limitation of movement of the left eye subsequently resolved, and the visual acuity improved to 6/5.

Discussion

The preceding case history plots the clinical course of a patient who sustained an eye injury which resulted in an undetected wooden foreign body remaining in his left orbit for a period of 14 weeks. Several factors prevented early recognition of the true nature of the orbital lesion.

The history elicited from the patient did not suggest direct penetration of the periocular tissues. He was aware of the branch merely brushing across his left eye and did not suspect any more serious injury.

The delay of 4 days before surgical repair could be carried out probably precluded any possibility of identifying such a deeply situated foreign body because of the profuse tissue swelling and closure of the subconjunctival tract along which the wooden twig had passed. Exploration of the wound did not reveal any subconjunctival extension beyond the immediate confines of the conjunctival laceration, and apart from several particles of dirt no significant foreign body was apparent.

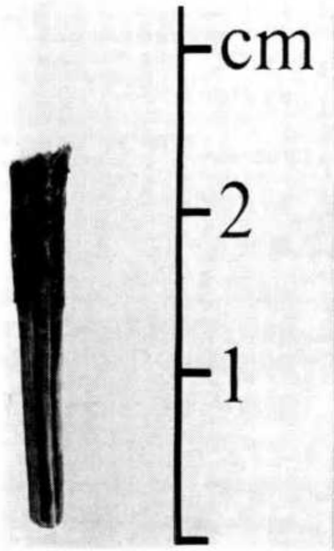

Fig. 5 *The wooden twig removed from the left orbit*

The conjunctival chemosis was consistent with the tissue trauma, particularly in view of the delay between the injury and wound repair. Furthermore, in the absence of proved infection, the persistence of the chemosis could have been the result of prolapse and desiccation of the conjunctiva.

Limitation of movement of the left eye could have been attributed to the mechanical restriction imposed by the bulbar conjunctival chemosis and also interference with extraocular muscle function by increased tissue tension. In retrospect, both the chemosis and interference with the movement of the left eye were the direct consequence of the granulomatous reaction induced by the wooden foreign body. Orbital radiography was unhelpful because of the radiolucent nature of the wooden foreign body.

The CAT scan was equivocal. The increased density noted in association with the left lateral rectus muscle was probably the manifestation of a granulomatous myositis, and the enhancement which followed the injection of contrast medium was in keeping with this interpretation. The foreign body was not positively identified by the CAT scan for several reasons. The foreign body lay close to the orbital floor possibly within the 'blind area' of the CAT scan described by Gawler *et al.* (1974). The situation of the twig, adjacent to and parallel with the inferior rectus muscle, and also the similarity in dimension and density to the muscle, would render localisation virtually impossible by standard CAT scanning techniques.

The failure of ultrasonography to localise the foreign body can also be explained in terms of its position. The close proximity of relatively dense tissues with good sound-reflecting interfaces possibly masked the foreign body to the sound wave. Furthermore, the sound emission from the ultrasonic probe would be directed towards the broken end of the twig, a structure 4 mm in diameter, surrounded by tissue of similar density. The foreign body would therefore possess poor sound reflecting properties and would produce a correspondingly weak echo, rendering ultrasonic diagnosis most unlikely. The case dramatically illustrates the limitations of both CAT scanning and ultrasonography in the diagnosis and localisation of a wooden foreign body situated in the orbit.

The presence and situation of a retained orbital foreign body were suggested by the fundus appearance of a scleral buckle on indirect ophthalmoscopy. However, it was the administration of corticosteroid therapy which brought about sufficient reduction in the inflammatory reaction to permit positive localisation of the anterior end of the twig by palpation through the lower eyelid. These findings provided adequate direct localising evidence to justify the surgical exploration which ultimately led to the removal of the foreign body.

The anti-inflammatory effect of corticosteroid therapy produced 2 distinct clinical benefits. Firstly, the foreign body, which had previously been masked by tissue swelling, was revealed to the palpating finger when the swelling subsided. Secondly, the surgical approach to the foreign body was rendered less hazardous by a reduction in the granulomatous reaction and conjunctival chemosis. In this particular patient the administration of systemic corticosteroids was therefore of diagnostic and therapeutic value, though the decision to start such therapy was originally made on an empirical basis.

When a patient presents with a history of an ocular injury caused by organic material such as wood, the possibility of a retained orbital foreign body must be considered, particularly when inflammatory signs persist and limitation of ocular movement is evident. The indication of a normal orbit by CAT scanning or ultrasonography does not exclude a retained wooden foreign body. However, as Duke-Elder (1972) stressed, it should be considered potentially hazardous to embark on a blind exploration for a suspected orbital foreign body without positive proof of its position or even of its existence. In circumstances as illustrated by the case described it is prudent to temporise until definite localising signs become apparent before surgical exploration is contemplated. Such management facilitates a planned surgical approach, thus minimising the operative trauma to the orbital structures.

I am grateful to Mrs A. Gearce for secretarial services and to Mrs A. Ellingford and Mrs R. McNeil for the preparation of photographic material.

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Book reviews

Membrane Transport in Biology. Vol. 3. Transport Across Multi-Membrane Systems. Ed. G. GIEBISCH, D. C. TOSTESON, and H. H. USSING. Pp. 459. DM148. Springer-Verlag: Berlin. 1978.

This volume is one of a series intended primarily for the general physiologist, and the contributions cover a wide field, including not only most animal epithelia but also transport systems in plant cells. Only 3 sections are of immediate interest to the ophthalmologist, namely, 2 chapters by J. A. Zadunaisky on transporting epithelia in the eye and 1 by J. H. Thaysen on the lacrimal gland. Of the contributions from Zadunaisky, Chapter 10, which deals with transport in cornea and lens, is probably the better of the 2 and includes a useful account of the author's own studies on amphibian tissue. Chapter 11, on ciliary epithelium and retinal pigment epithelium, is rather less satisfactory. The part devoted to pigment epithelium occupies barely 2 pages, although the author describes in some detail the vacuolation cycle for transport across the wall of Schlemm's canal, a process which, strictly speaking, concerns endothelium rather than epithelium. Some of the references are incomplete and in one or two cases the citations in the text are incorrect. Chapter 14, by J. H. Thaysen, provides a very useful account of current work on lacrimal secretion. Apart from these specialised sections the first 3 chapters of the book form a useful introduction to the electrophysiological and ultrastructural aspects of epithelial transport.

D. F. COLE

Documenta Ophthalmologica Proceedings. Genesis of Glaucoma, Wessely Symposium, Munich, 1974. Vol. 16. Ed. H.-J. MERTE. Pp. 320. $51·00. Junk: The Hague. 1978.

This volume contains the proceedings of the Wessely symposium held in Munich in 1974. The delay in publication reflects the difficult task of editing the contents of a meeting which was given almost entirely to discussion. There were no formal papers, but the main contributions in discussion have been compiled by the authors into short articles, and these are interspersed with sequences of verbatim discussion.

The book is divided into 2 parts. The first, on the physiology and pathology of intraocular fluid exchange, contains 20 papers together with discussion on subjects as varied as the formation of aqueous humour and malignant glaucoma. The second part contains 15 papers and discussion on the pathogenesis of disc cupping and visual field defects. Finally there is a summary and overview of the meeting by its chairman, Hans Goldmann.

With a few exceptions the individual papers are of interest. Some provide a useful review of the subject under consideration, while others, for example Paul Henkind's philosophical dissertation on the pathophysiology of glaucoma field loss, highlight current controversies. It is the discussion sequences, however, that best reflect the nature of the meeting, and these provide illuminating and often entertaining reading. So although the symposium was held 5 years ago these proceedings justify the effort of their production and are a useful addition to the literature on glaucoma.

ROGER COAKES

Clinicopathologic Correlation of Ocular Disease: A Text and Stereoscopic Atlas. 2nd edn. By DAVID J. APPLE and MAURICE F. RABB. Pp. 526. £78·75. YB Medical Publishers: London. 1978.

Because biopsy of intraocular tissues is rarely feasible, the most useful contribution of histopathology to ophthalmology is not so much in diagnosis as in providing an improved understanding of the nature of specific eye diseases. To explain the symptoms experienced by individual patients in terms of the causative disease process is much of what pathology is all about. Moreover, a proper appreciation of the lesion—its nature and expected behaviour—is fundamental to rational management. It is a cause for congratulation, therefore, when an attempt is made to take pathology from the laboratory to the ward, to go beyond regarding pathology merely as a means towards applying or confirming diagnostic labels, and to relate microscopical appearances to clinical practice.

The superbly illustrated text by Drs Apple and Rabb is a brave and largely successful attempt in this direction, as the emergence of a second edition after only 4 years bears witness. The text is concerned primarily with relating the clinical and histopathological appearances of ocular disease and is well served by 112 excellent stereoscopic colour transparencies tucked inside the back cover and 758 monochrome illustrations of generally good quality. The correlation would have been even more satisfying, however, had more space been devoted to the functional basis for the altered tissue morphology: for instance, an awareness of some of the factors involved in producing neovascularisation has just as much clinical significance as a knowledge of its form and complications.

After a brief introduction to ocular anatomy and embryology and a useful account of the developmental anomalies there follow 8 chapters providing a fairly comprehensive coverage of ocular diseases. A chapter dealing with the optic nerve has been added, and those on the lens and glaucoma have been separated and expanded since the first edition. Inevitably the authors sometimes hold views which are not always shared by the reviewer, but this does not necessarily imply criticism, the text being throughout balanced and reliable and adequately supported by well-chosen references.

Those who valued this book when it first appeared will need no urging to examine the updated version, and it is to be expected that it will win many more admirers.

ALEC GARNER

Lens Ageing and Development of Senile Cataracts. Ed. O. HOCKWIN. Pp. 294. DM139. Karger: Basel. 1978.

This is one of a series (No. 12) of Interdisciplinary Topics in Gerontology. It runs to 294 pages, with 170 figures and 47 tables. The volume consists of 30 papers presented at a 'workshop' on the ageing of the lens held in Bonn in 1977.

The papers are diverse, largely biochemical, and almost exclusively report studies on animal lenses or on cell cultures derived from animal lens epithelium. As might be expected, most of them are concerned with the lens proteins, but the components of lens capsule, the morphology of lens epithelium, the water content, the cation distribution, and enzyme activity in relation to aging form the subject matter of one or more papers.

As a compilation of current work at the time of the workshop and on the direction of future research trends in this field the book must be of interest to all those working in lens chemistry. It is, however, unlikely to be of more than limited interest to general ophthalmic readers. The book is well printed and well indexed and should form a good up-to-date source of reference to those working in this field. W. S. FOULDS

Visual Impairment in the Schools. By RANDALL K. HARLEY and G. ALLEN LAWRENCE. Pp. 153. $10·75. Charles C. Thomas: Springfield, Illinois. 1977.

The dust cover of this book states that 'between these covers one will find a succinct and easily understood guide . . .'. Unfortunately this is not true.

The book is divided into Part 1, 'The eye and its diseases', and Part 2, 'Education of low vision children'. There is an appendix and a glossary. Part 1 is unclear, inaccurate, and riddled with unexplained jargon. Even if one forgives the proof reader his failure to ensure that the numbers in the text refer to the correct diagrams, these are badly drawn, too complicated, with hand written labels sloping in all directions. Part 2 is in the main well written and informative. It starts with a good review of vision screening procedures in normal and low ability children; then follow chapters on the visual environment, optical aids, the educational implications of the commoner eye conditions, and a simply written chapter on visual and perceptual development.

There is a clear need for a book such as this for teachers and therapists. If the first half of the book had been as good as the second, this would have been it.

BARRY JONES

Immunology of Uveitis and Ocular Tumors. By DEVRON H. CHAR. Pp. 122. $15·00. Grune and Stratton: New York. 1978.

This attractive text published in the series of 'Current Ophthalmology Monographs' is intended to help the ophthalmologist understand the immunological aspects of eye disease. The author is director of the ocular oncology unit at the Francis I Proctor Foundation Department of Ophthalmology at the University of San Francisco.

The first chapter describes the basic concepts of immunology—the immunoglobulins and their biological role, the complement system, macrophages and lymphocytes, antigen processing, and the immune response in a general way. Then follows a discussion of HLA antigens and eye disease, experimental models of uveitis in the laboratory and in man, the role of immunological testing in uveitis, and the use of cytotoxic drugs and of steroids in the treatment of uveitis. These chapters are well written, informative, and well referenced.

Just under half the text is concerned with immunology in relation to tumours of the eye, an aspect of ophthalmology with which the author has substantial experience. Attention is drawn to certain established facts—the occasional spontaneous regression of retinoblastoma and choroidal melanoma; that conjunctival and uveal melanoma may remain stationary for a long time before unequivocal clinical evidence of growth is apparent; the long interval that may occur after excision before there is evidence of metastatic disease; that a large proportion of apparently incompletely excised basal cell carcinomata of the eyelids do not recur; and that the presence of circulating malignant cells in cases of retinoblastoma at enucleation does not always indicate a bad prognosis. These observations may reflect immunological action in the host-tumour relationship. The final chapter considers the present role of immunotherapy and future prospects for immunological techniques in the differential diagnosis and treatment of patients with ocular tumours. There is a useful glossary of immunological terms.

This short well written monograph is strongly recommended. P. A. MACFAUL

Progress in Anterior Eye Segment: Research and Practice. Documenta Ophthalmologica Proceedings Series. Vol. 18. Eds. O. Hockwin and W. B. Rathbun. Pp. 370. No price given. Junk: The Hague. 1979.

This volume is in honour of Professor John Edward Harris, of the University of Minnesota. The papers reflect his life-long interest in the metabolism of lens and cornea. There is a great deal of information for those who are particularly interested in the biochemical changes which occur with ageing of the lens and the formation of cataract. Two papers deal with the effect of ultraviolet light on the lens and factors affecting light transmission.

The papers dealing with the cornea include current concepts on corneal transparency and clinical papers on cystinosis and Fuchs's dystrophy. The volume is concluded with the surgical treatment of epithelial cysts in the anterior chamber. R. F. FISHER

Ocular Pathology. 3rd edn. By C. H. GREER. Pp. 281. £13·50. Blackwell: Oxford. 1979.

Since its first appearance in 1963 Dr Greer's book has won a well-deserved place on the reading list of many practitioners of ophthalmology in this country and elsewhere, and this updated third edition will doubtless be welcomed by a new generation of students entering for the FRCS and DO examinations.

Although the content is essentially as in the previous editions, there are few topics which do not show evidence of revision. Some sections, such as those dealing with immunity and allergic reactions, with fungal and chlamydial infections, with precancerous epidermal lesions, with corneal dystrophies, and with the vascular retinopathies, have been expanded slightly. Electron microscopy is introduced. albeit to a very limited extent, for the first time. The overall length of the book is nevertheless almost the same as that of the previous edition owing to pruning of obsolete material. Unfortunately, while some figures have been replaced, there are still too many inferior photomicrographs.

This is a reliable and lucid introduction to eye pathology which can be recommended to students with confidence. A. GARNER

Praktische Glaskörperchirurgie. By JEAN HAUT and SYLVIE LIMON. Pp. 166. DM54. Enke: Stuttgart. 1978.

Vitreous surgery is advancing so rapidly that it is sometimes difficult to keep up with the new instrumentation and techniques of this fascinating branch of ophthalmology. 'Practical vitreous surgery' is a German translation of a book originally published in French. Unfortunately between the time of the initial text and the final translation many major advances have occurred, with the inevitable consequence that the book is sadly out of date. There is no reference to work after 1971, and thus all the revolutionary techniques of closed vitreous surgery are missing. Nevertheless this volume provides much useful and interesting information about basic vitreous physiology and pathology, and at the time of its original publication it provided a rational appraisal of contemporary surgical procedures concerning the vitreous, especially in the management of vitreous loss during cataract surgery. Ophthalmic surgeons without access to modern vitrectomy instruments will find the chapters on 'open sky' techniques valuable, but the book is unlikely to have a general popular appeal. T. J. FFYTCHE

Ophthalmology Study Guide for Students and Practitioners of Medicine. 3rd edn. Joint Committee on Medical Student Education. Pp. 196. No price given. American Academy of Ophthalmology and Otolaryngology: Minnesota. 1978.

This guide to 'patient problem-areas' and 'important concepts of diagnosis and management in the field of eye care' is written to supplement the various standard primers of ophthalmology. Rather like a breviary, it selects from the established ophthalmology bibles (to which the student is throughout referred) aspects which need amplification and it gives general guidance to practice. It is well laid out, with lists of questions and a loose plate of micro-fiches (a sheet of miniature coloured transparencies).

The traditional English student might cavil at the rather hectoring approach, the prolixity, the polysyllables, the jargon, the sociological catch-phrases, and so on, but I am sure that the authors know the sort of language to which their students respond best; and there are indeed many felicities and aphorisms that lighten the ever-insistent 'problems' and 'situations'. Odd statements also sometimes take one aback. Thus on starting off with section 1 (headed 'Visual Acuity'), subsection 1 (headed 'Relevance'), macular degeneration is quoted as the first of the 'Blinding eye diseases which may be treated and vision restored'.

But these limitations should not detract from the central virtue of this book, which is to provide a new dimension to ophthalmology as it is gleaned from the standard textbook, like a template, filling in its gaps and ambiguities, highlighting, clarifying, and consolidating. It is an original approach, and many an eye doctor will be the wiser after reading it. P. D. TREVOR-ROPER

Taschenbuch der Augenheilkunde. By H. J. KÜCHLE and H. BUSSE. Pp. 408. DM68. Verlag Hans Huber: Bern. 1978.

Handbooks of ophthalmology are always welcome, and when they succeed in condensing an exhaustive number of facts under one cover they are to be congratulated. This small compact volume (less than 400 pages) is comprehensive enough to serve as textbook for undergraduate and postgraduate students and also to provide a ready reference book for practising ophthalmologists. There are sections on basic physiology, pathogenesis, and treatment of common and uncommon ocular disorders, though surgical techniques are not discussed in detail. More important for those revising for examinations, there are lists and tables and a glossary of over 250 syndromes. Unfortunately there are very few illustrations, and many of the treatments have a strong Continental flavour, but these are minor criticisms of this splendid little book. If it were translated into English it would certainly find a place in most eye departments and consulting rooms as well in the pockets of postgraduate students. T. J. FFYTCHE

Intraocular Lenses. By RONALD A. SCHARCHAR. Pp. 133. $16·75. Charles C Thomas: Springfield, Illinois. 1979.

If there has been, over the last 30 years, an ophthalmic surgical subject fraught with controversy, then the subject of this book must certainly be the one. This controversy has arisen largely because of the refusal or inability of those persons connected with its development to apply to its study the level of scientific critical assessment it required. So outstandingly encouraging were the results obtained in favourable cases that those that fell short of this attainment tended to be disregarded. As the failed cases became the responsibilities of other surgeons, so factions strongly for and against intraocular implants came into being.

Over the last 10 years responsible surgeons have made a vigorous effort to correct this disastrous state of affairs. Scientific methods have been applied to implant design, to surgical techniques, to case analysis, and to the study of complications and how they may be avoided. Useful progress has been made. This form of surgery now has a place in ophthalmology which can be described as both ethical and valuable.

With this in mind it is desirable that comprehensive contributions to the relevant literature should be seen to build on this late foundation and not to turn the clock either back or too far forwards with ill-advised haste. In this respect, this book falls short of what is required. It represents a very personal account of Dr Scharchar's views, with much detail about his surgical techniques and the value of his design of implant. His views are unsupported by statistical evidence of his own, and no mention is made of the need to make further study and assessment of results and complications in a proper scientific manner.

Because of the number of astonishing and possibly dangerous assertions such as that α-chymotrypsin causes glaucoma and delayed wound rupture, or that endothelial dystrophy does not constitute a contraindication to implant surgery, this book should be regarded as unsuitable for postgraduate study, unless read with well-developed critical faculties. The text is not assisted by medical illustrations of poor quality.

This book reflects an attitude in favour of implantation for almost every type of patient with cataract and belittles the disadvantages, attributing most complications to faulty surgical technique rather than to unsatisfactory clinical judgment. Such teaching could easily lead the inexperienced surgeon and his patients into serious trouble.

A. D. MCG. STEELE

Colour Vision. By GERALD S. WASSERMAN. Pp. 224. £13·40. John Wiley: Chichester. 1978.

This useful historical review will be of interest to both the expert and the layman. It is eclectic in the sense that it starts with Newton, even though the study of colour vision received a considerable impetus a century and a half earlier at the hands of Leonardo da Vinci. The author spends quite some time in grappling with psychological concepts—a thankless task, in your reviewer's opinion. His description of fundamental physiological studies on primates is brief to the point of being curt, but perhaps this restores a recent imbalance in the literature on colour. It is interesting to witness the resuscitation of long-laid ghosts, and to see recent ones confirmed. For example, the so-called principle of univariance (p. 91), linked with Rushton's name, was stated by Einstein at the beginning of this century and really stems from photochemical principles datable to the middle of the last century. But if we credit someone with a discovery often enough he will make it one day.

R. A. WEALE

Correspondence

Experimental branch retinal vein occlusion

SIR, I was interested to read the 3 publications[1-3] in the June 1979 issue of the *British Journal of Ophthalmology* on experimental branch retinal vein occlusion (BRVO). We have had similar results in our identical experimental studies on BRVO, conducted over the past 6 years, with a follow-up of eyes in rhesus monkeys up to 2 years (not published as yet). While I support, in general, the findings of the authors on BRVO, I take very strong issue with some of the statements regarding our work on central retinal vein occlusion (CRVO) by Hamilton *et al.*[1] and particularly in the anonymous editorial[4] preceding that paper.

The editorial[4] appears to make the mistake of equating CRVO with BRVO. The articles describe studies of BRVO and *not* CRVO, and the author of the editorial has drawn conclusions from those studies on the BRVO only. CRVO and BRVO are 2 very distinct conditions. The anatomy of the CRV, the various physiological and pathological aspects of its blood flow, and the pathogenetic factors in its occlusion are very different from those of the BRV. Moreover, studies reported do not even reproduce all aspects of the clinical syndrome of BRVO in the animals. To apply the findings to CRVO (without doing any exhaustive studies on CRVO) is in my view ridiculous.

In the field of research, the emergence of new facts and evidence makes us modify our views as we go along, provided we keep an open scientific mind. My studies, conducted in the early 1960s and published in 1965,[5] were conducted on a small series and, more importantly, before the advent of fluorescein angiography and it was impossible to determine the extent and type of occlusion of retinal vessels under those experimental conditions. Our recent studies[6] clearly revealed the limitations in those earlier studies, and the consequent erroneous impressions. Recently we pointed out[6] the discrepancy in the 1965 study in the light of our recent findings, but the author of the editorial has taken no notice of that fact. The editorial writer even misrepresents our current views on the subject.

According to the author of the editorial, 'the difference in the clinical appearances [between the CRVO and BRVO] are due to differences in the site of the obstruction'. Site of occlusion undoubtedly plays an important role in the severity of the clinical picture of CRVO, and we strongly emphasised this fact in our paper,[6] but that does not explain everything about the pathogenesis of CRVO. For example, one-third of the patients with CRVO have ocular hypertension or chronic simple glaucoma, whereas in BRVO the incidence is *no* higher than in the general population.

The author admits the presence of 'ischaemic capillaropathy'. This can be reproduced by more mechanisms than one. No doubt isolated venous occlusion by itself (if no significant collaterals exist before the site of occlusion) can produce it, as is evidently the case in BRVO and in a number of cases of CRVO (if the site of occlusion in the latter is at the lamina cribrosa or close to it, and no collaterals are available). In my paper in 1971[7] (on page 1009) I stated that 'in some cases, primary retinal venous obstruction in the closed retinal circulation may produce secondary retinal arterial insufficiency'. However, other factors can also produce retinal ischaemia, even if the site of occlusion in the CRV is somewhat further back. A transient retinal ischaemia seems to play a very important role in the majority of patients with CRVO. There is clinical and experimental support for this. Among the patients with CRVO there is a high incidence of cardiovascular disorders, and patients with these abnormalities develop marked systemic arterial hypotension during sleep. It is well known that a vast majority of nonembolic arterial occlusive episodes in the brain and eye develop during sleep (e.g., cerebral stroke, anterior ischaemic optic neuropathy, central retinal artery occlusion), so that the patients discover them on waking in the morning. Transient arterial hypotension and consequent fall of perfusion pressure leads to transient ischaemia for a few hours. Similarly, in CRVO, ischaemic insult develops most often during sleep, and in the majority the visual defect is discovered on waking up in the morning. Fluorescein fundus angiography, even a few hours after the discovery of defective vision, shows a fairly reasonable arterial circulation because of the recovery of systemic blood pressure. A normal arterial blood flow, on fluorescein fundus angiography, further indicates that there is no organic occlusion of the central retinal artery in these eyes. *To get this transient retinal ischaemia one does not require central retinal artery occlusion—in fact, there is no central retinal artery occlusion in these eyes.* In our recent experimental studies[6] we used transient clamping of the central retinal artery *simply as an experimental means to produce transient ischaemia, and did not imply at any time that there was an organic central retinal artery occlusion in a clinical situation.* To attribute a statement like 'progressive capillary closure in retinal vein occlusion is due to arterial occlusion' to us[6] represents either gross ignorance of our work or deliberate misrepresentation. In fact, we mention 'retinal ischaemia' as a most probable cause of capillary obliteration—a view currently accepted on the subject, and also admitted in the editorial. It is worth pointing out that on serial sections of the optic nerve in an eye with CRVO Stowe *et al.*[8] showed *a definite occlusion of both the central retinal artery and vein.* This would represent an occasional eye with CRVO, where in fact there could be an organic occlusion of the artery in addition to the occlusion in the CRV, as was thought in my original study.[5]

Thus, this editorial did not at all do justice to our latest view[6] on the subject of the pathogenesis of CRVO; but in fact misrepresented us. To set the record straight, let me restate our current views[6]. In the pathogenesis of CRVO there is *no* organic occlusion of the central retinal artery, but there is a *transient retinal ischaemia* which 'acts as a triggering mechanism in an already diseased CRV predisposed to haemorrhagic retinopathy'[6]; and while the site of occlusion in CRVO is an important factor, it is not the only factor in the pathogenesis of the CRVO, which is 'multifactorial'. To lump CRVO and BRVO into a single entity of 'retinal vein occlusion' has no justification whatever, and represents a serious error of judgment leading to all the confusion.

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[5] Hayreh SS. Occlusion of the central retinal vessels. *Br J Ophthalmol* 1965; 49:626–45.

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SIR, The misinterpretation of Mr Hayreh's paper[1] was certainly not deliberate. If it was misinterpreted this occurred because the points raised were not very clearly put in the original paper. In that paper Mr Hayreh repeatedly talks about transient arterial stasis or occlusion—for example, on p. 318 in the first column; on p. 320 in the first column; on p. 321 he suggests that arterial insufficiency acts as a trigger mechanism in the already diseased central retinal vein (CVR). Obviously, I assumed that he meant that the ischaemia of the capillaries was secondary to the arterial disease. I am sorry if this is not what he meant.

It appears that Mr Hayreh's and our own views are really not as different as they used to be and there is considerably more agreement between us than there was before. Nevertheless, I stand by our Group's opinion that: (1) The clinical picture of both CRV occlusion and BRV occlusion is produced by outflow obstruction and the differences in appearance are due to the differences in siting of the occlusion. Chronic simple glaucoma in CRVO does not alter my views; it is just one factor which contributes to or precipitates venous stasis—probably when flow is at its lowest, intravascular pressure is at its lowest and intraocular pressure at its highest. (2) The disagreement between us, which is now very narrow, is on the production or pathogenesis of ischaemic capillaropathy. We suggest that the primary lesion is in the vein and that raised intravascular pressure, secondary to outflow obstruction, causes stasis and ischaemia and the clinical picture. This is what our experiments confirmed and we believe it to be so in the human situation as well.

I certainly am glad to see Mr Hayreh alter his views in the light of recent experimental evidence and I can assure him that the misinterpretation was not deliberate but a genuine misunderstanding of some of his statements.

EVA KOHNER

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Reference

[1]Hayreh SS, van Heuven WAJ, Hayreh MS. Experimental retinal vascular occlusion—I. Pathogenesis of central retinal vein occlusion. *Arch Ophthalmol* 1978; 96:311–23.

[This correspondence is now closed.—ED, *BJO*.]

Obituary

John Scully, MD, DPH, DOMS

Dr John Scully, who died earlier this year, graduated from Manchester Medical School in 1931 and in the 1930s was appointed oculist to the then Salford Education Department. Thereafter, apart from a break for war service in the RAMC, he devoted himself to the care of children with visual defects and squint in this area. This work continued in the Salford Area Health Authority (T) team until his reluctant retirement a few months before he died.

In 1968 he received the MD from the University of Manchester for work on the epidemiology of squint and amblyopia. He had a long association with the Royal Eye Hospital in Manchester, where he was SHMO, and he remained an honorary clinical assistant at this hospital until his death. He was a very kindly and unassuming doctor and is remembered with affection by many of his young patients and their parents.

Notes

Glaucoma congress

The International Glaucoma Congress and the American Society of Contemporary Ophthalmology will hold their joint annual meeting in Orlando, Florida, on 9–15 March 1980. Details from Dr John Bellows, American Society of Contemporary Ophthalmology, 6 North Michigan Avenue, Room 1110, Chicago, Illinois 60602, USA.

Retinal detachment surgery

'Retinal detachment surgery—strategy and tactics' is a course approved for 14 hours of CME I credit, sponsored by the Manhattan Eye, Ear and Throat Hospital and scheduled for 14–15 March 1980. Further information from James S. Schutz, MD, Manhattan Eye, Ear and Throat Hospital, 210 East 64th Street, New York, NY 10021, USA.

Consilium Europaeum Strabismi Studio Dedtium

The 11th meeting of the CESSD will take place at the Institute of Child Health, Guilford Street, London WC1, on 18–19 April 1980 prior to the European Ophthalmological Congress in Brighton. Details from Miss Barbara M. Lee, Moorfields Eye Hospital, High Holborn, London WC1 7AN.

Cadaver lacrimal surgery

The sixth annual Boston lacrimal course, newly expanded with inclusion of cadaver lacrimal surgery, will be held on 5–6 June 1980 in Boston. Details from the Office of Continuing Education, Boston University School of Medicine, 80 East Concord Street, Boston, Mass. 02118, USA.

Ultrasound

The 8th symposium of the Societas Internationalis de Diagnostica Ultrasonica in Ophthalmologia (SIDUO) will be held in Nijmegen, Holland, on 16–19 September 1980. Details from Dr Johan M. Thijssen, St Radboudhospital, 6500 HB Nijmegen, Holland.

European Ophthalmic Pathology Society

The European Ophthalmic Pathology Society held its annual meeting in Brussels on 14–17 May 1979. Dr Hugh Greer, of Melbourne, Australia, was the guest of honour. The scientific programme included 39 case presentations by members and guests, and 17 countries were represented. For each presentation a protocol, histopathological sections, and appropriate clinical or macroscopic transparencies were provided.

The majority of case presentations dealt with inflammatory and metabolic disorders involving the globe, orbit, or eyelid, and the discussion was concerned predominantly with the nature of the biochemical disturbance. Malignant disease was also a prominent subject of the presentations, and the remainder of the cases provided examples of congenital malformation of the ocular tissues.

The 33 members who attended were: K. Arnesen (Norway); N. Ashton (UK); J. Babel (Switzerland); E. Balestrazzi (Italy); D. R. Barry (UK); P. Bec (France); M. Brihaye van Geertruyden (Belgium); A. Brini (France); J. G. Cunha-Vaz (Portugal); B. Daicker (Switzerland); P. Dhermy (France); P. C. Donders

(Holland); H. Fanta (Austria); A. Garner (UK); A. Hamburg (Holland); M. Hanseens (Belgium); A. Henriquez (Spain); O. A. Jensen (Denmark); E. Kock (Sweden); E. Landolt (Switzerland); W. R. Lee (UK); O. Litricin (Yugoslavia); O.-E. Lund (BRD); W. A. Manschot (Holland); J. Mullaney (Ireland); G. O. H. Naumann (BRD); A. H. Nover (BRD); M. Quintana (Spain); R. Seitz (BRD); F. H. Stefani (BRD); A. Tarkkanen (Finland); D. Toussaint (Belgium); M. Vogel (BRD). Dr S. Ry Anderson (Denmark) and Dr G. Morgan (UK) were unable to attend. The five guests attending were R. Haddad (Austria), J. Libert (Belgium), H. Offret (France), J. G. Orsoni (Italy), and F. Weber (Switzerland). Dr A. H. S. Rahi (UK) was elected to membership.

Dr Daniel Toussaint (Belgium) acted as host for the meeting, and his excellent organisation also included a stimulating and enjoyable social programme. Princess Paola of Liège granted her patronage to the meeting and graciously attended both the reception and the annual dinner.

The next meeting of the society will be held in Stockholm, Sweden, with Dr E. Kock as organising secretary.

Change in style of references

In accordance with the Vancouver agreement many medical journals are to standardise the instructions they issue to authors on the preparation of articles. References will be cited by the numerical system already familiar in many journals, including the ***British Medical Journal***.

A paper (or book) cited in the text is referred to there by a superscript number. In the list of references the papers (or books) appear in the numerical order in which they are first cited in the text, not in alphabetical order by authors' names. For convenience in preparing the typescript the reference number may be typed between parentheses on the line, not superscript. The titles of journals will be abbreviated in accordance with the style of ***Index Medicus***. In the typescript they should either be abbreviated in that style or given in full. This journal will change to the numerical system from the first issue of 1980. ***Authors submitting papers are asked to adopt it now in order to facilitate editing.*** Three examples follow:

1. Green A B, Brown C D, Grey E F. A new method of measuring the blood glucose. ***Br J Ophthalmol*** 1980; **64**:27–32.
2. Green A B, Brown C D. ***Textbook of Medicine.*** London: Silver Books, 1980.
3. Grey E F. Diseases of the pancreas. In: Green A B, Brown C D, eds. ***Textbook of Medicine.*** London: Silver Books, 1980; 349–362.

Copies of the Vancouver agreement (50p, post free) are obtainable from the Publishing Manager, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR.

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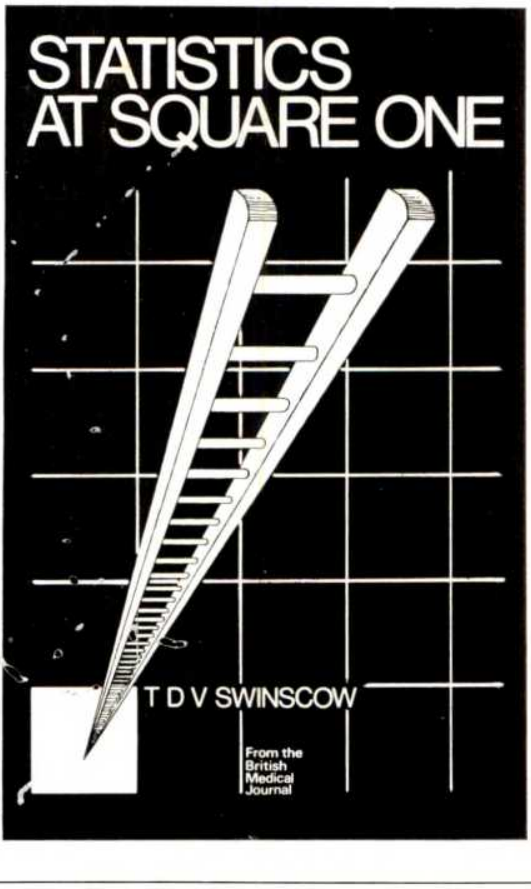

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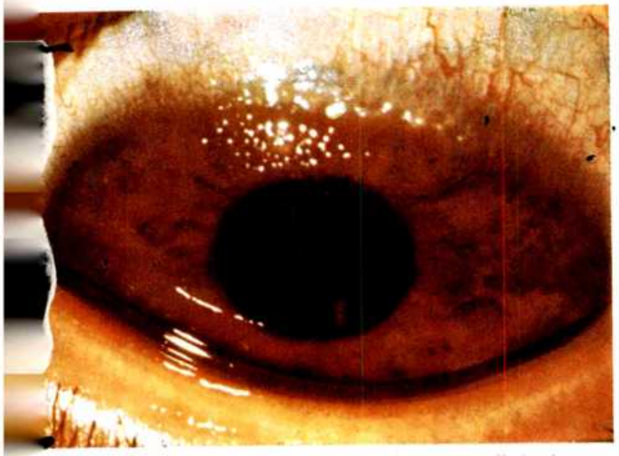

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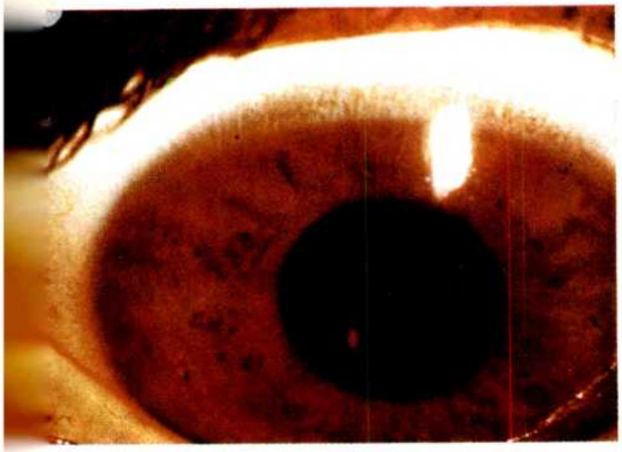

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